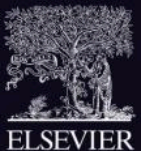


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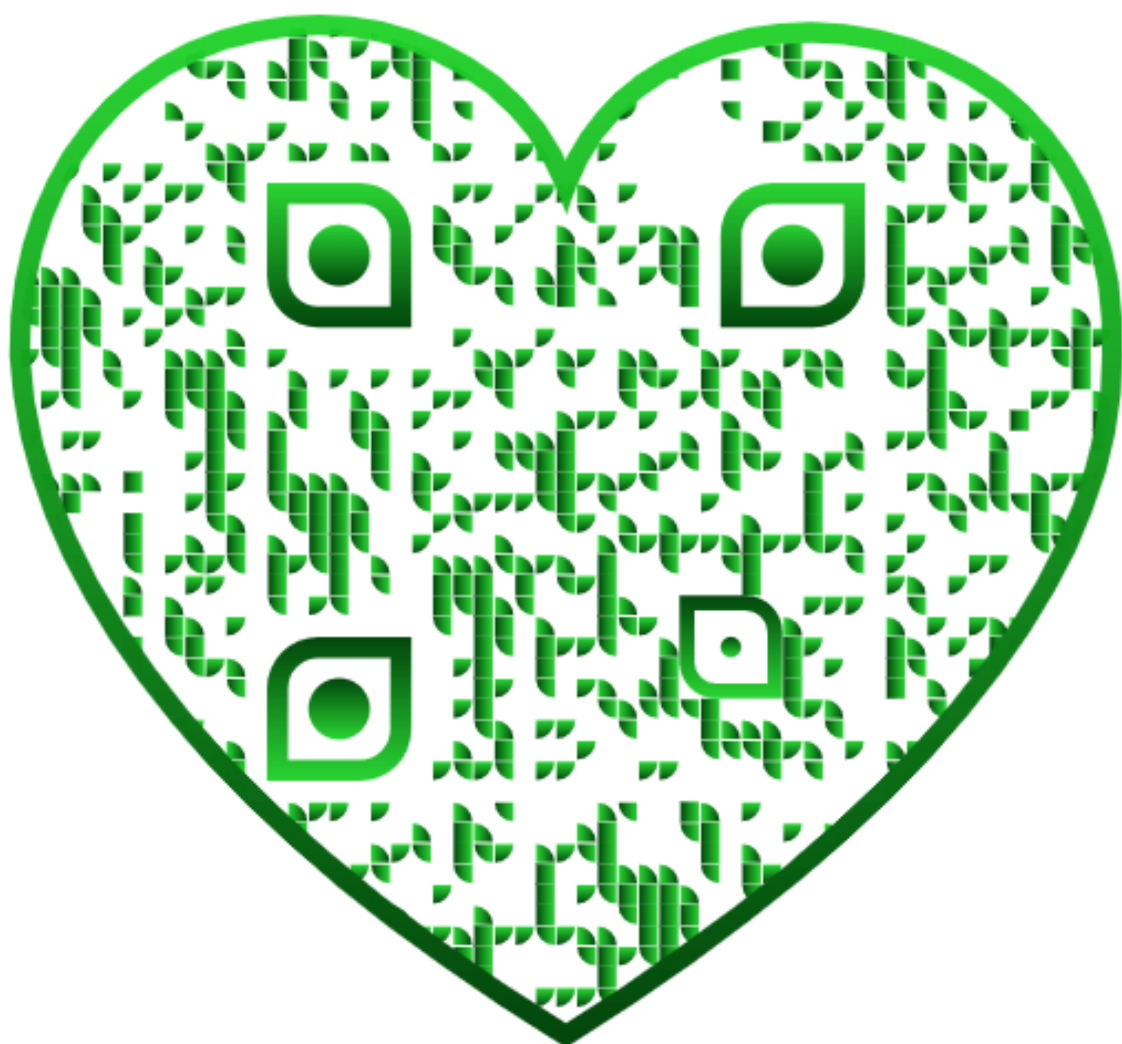
Rau's RESPIRATORY CARE PHARMACOLOGY

DOUGLAS S. GARDENHIRE



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Rau's Respiratory Care Pharmacology

ELEVENTH EDITION

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RAU'S RESPIRATORY CARE PHARMACOLOGY, ELEVENTH EDITION

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*To ALL respiratory therapists that served during the pandemic, thank you for showing the world
our worth and expertise!*

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Preface

Rau's Respiratory Care Pharmacology, 11th edition, provides the most exhaustive and up-to-date information pertaining to the field of respiratory care pharmacology. The importance of this text stems from the ever-changing nature of the field. The improvement of existing drugs and the creation of new drugs that use the direct access that the lungs provide to the human body have expanded the types of drugs respiratory therapists are using today and will use in the future. This book provides the respiratory therapy student with a strong foundation of the drugs presently used in respiratory care. It also serves as a valuable resource for the respiratory care practitioner.

Organization

The text is organized into three specific, fully referenced, comprehensive sections to allow the reader easy access to a particular section of interest. Unit One covers the basics of respiratory care pharmacology, including the principles of drug action, the basic methods of drug administration, the standard drug calculations, and the effects of drugs on body systems. Unit Two covers the drugs most frequently delivered to patients by respiratory therapists. Unit Three covers the drugs used to treat critical care and cardiovascular patients, featuring an entirely new chapter on the role of the respiratory therapist in the emerging area of sleep and sleep pharmacology.

Distinctive Features

- For more than 30 years, *Rau's Respiratory Care Pharmacology* has been the preeminent respiratory care pharmacology text. In their passion for excellent patient care in the field of respiratory care, Dr. Gardenhire and his team of notable contributors are committed to engaging the reader.
- The up-to-date material reflects changes in the field and prepares students for careers as respiratory therapists in today's health care environment.
- Comprehensive coverage provides the most thorough explanations of any respiratory care pharmacology text on the market.
- Pharmacokinetic principles are discussed as they relate to respiratory agents, drug administration, and a range of specific drugs used in respiratory care and their effects on body systems.
- Consistent organization throughout and helpful learning tools give students the optimal opportunity for knowledge and growth.
- A thoroughly revised Student Workbook provides extra opportunities for review and self-assessment.

New to this Edition

- Continued improvement in readability provides greater comprehension of this complex material.

- The addition of more clinical connections to assist the reader in the application of the agent in the clinical setting.
- Expansion of Evolve Learning Resources for respiratory therapy students includes electronic flashcards to assist study efforts and an NBRC Correlation Guide.
- Two appendices include a conversion chart for units and systems of measurement from customary US imperial measures to the metric system as well as a list of the most commonly prescribed respiratory medications and acceptable mixtures.
- New drug cards have been created to provide detailed information on agents in a simple accessible form.

Pedagogic Features

- A consistent approach within each chapter begins with Chapter Outlines, measurable Objectives, and Key Terms with definitions identifying key information. Key pharmacologic agents are covered, noting the dosage and administration, mode of action, pharmacokinetics, and hazards and side effects. Each chapter ends with a series of Self-Assessment Questions and a Clinical Scenario to help readers assess their comprehension of the material. Answers are provided in Appendix A at the back of the book.
- Learning Objectives that parallel the levels tested by the National Board for Respiratory Care (NBRC) examinations help identify important information that goes beyond memorization and recall.
- Key Terms with definitions provide easy access to the pharmacologic vocabulary the respiratory therapy student should embrace.
- Full-color illustrations throughout highlight special features and draw out relevant details.
- Key Points boxes, located throughout each chapter, highlight concepts with which the reader should become familiar while working through the material.

Ancillaries

For the Instructor

For the 11th edition, the Evolve Resources for *Rau's Respiratory Care Pharmacology* provide an interactive learning environment designed to work in coordination with the textbook. It features a test bank, PPTs, case studies, an image collection, and an NBRC Correlation Guide.

The Test Bank includes more than 600 questions. There are more than 500 PowerPoint slides that include embedded animations and Automated Response System questions. Evolve may be used to publish the class syllabus, outlines, and lecture notes; set up "virtual office hours" and e-mail communication; share

important dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards. Evolve allows instructors to post examinations and manage their grade books online. For more information, visit <http://evolve.elsevier.com/Gardenhire/Rau/respiratory/> or contact an Elsevier sales representative.

For the Student

The *Workbook for Rau's Respiratory Care Pharmacology* has been completely rewritten to provide a variety of exercises for each of the 23 chapters in the book. The tenth edition was reviewed and extensively revised to correspond with the learning objectives. All answers are referenced back to the text for ease in further review. Examples include NBRC-type questions, critical thinking exercises, case studies, definitions, and appropriate content

review to help break down the difficult concepts in the textbook. The workbook creates a more complete learning package for students and allows the student exposure to more questions in addition to what is available in the text. The answers for the exercises are located on the Evolve Resources. Ask your instructor for details.

The Evolve Student Resources include electronic flashcards to assist study efforts and an NBRC Correlation Guide.

The continuing developments in respiratory drugs and in related critical care drug groups, with the increasing complexity and scope of material, challenge practitioners, students, and authors alike. Every effort has been made to ensure the accuracy of information on drugs in this text. However, practitioners are urged to review the manufacturer's detailed literature when administering a drug and to keep themselves informed of new developments in drug therapy.

Acknowledgments

The 11th edition of *Rau's Respiratory Care Pharmacology* is dedicated to all RTs, including students that sacrificed during the pandemic to serve our fellow man when the need was so great! As with previous editions, this edition benefits from the substantial contributions of individuals who are experts in various areas of pharmacology and aerosol medicine. Their names and affiliations, too numerous to list here, are found in the list of Contributors. They have graciously provided invaluable material for this revised edition of the text. I thank all of them for their wisdom and kindness in preparing their chapters.

I want to thank all faculty, staff, and students of the Department of Respiratory Therapy at Georgia State University. Each of you is meaningful to me in both my personal life and my professional life. It is you who make the department a place that I look forward to coming to each morning. I could not do most of what I do or have done without your assistance!

I am grateful to the reviewers who provided me direction and clarification based on their experiences in the classroom and the hospital. I also appreciate the efforts of all those who worked so

tirelessly behind the scene to make sure that this book made it to market. I want to thank Kayla Jarman for always being available and assisting in the development of this edition! I want to congratulate Melissa Rawe for picking up where Yvonne left off. It was a great relief to transition to a familiar face when working on this new edition.

I want to thank my entire family for everything they do to support me! A special thanks to my Grandma, Erlene Cares, for always pushing for education and helping me be better than I truly am; you will be missed!

Finally I must recognize all of the students and therapists who have and will continue to learn from this textbook. Thank you for allowing me to be a small part of your career!

Douglas S. Gardenhire, EdD, RRT, RRT-NPS, FAARC

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

Mahatma Gandhi

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1

Introduction to Respiratory Care Pharmacology

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Pharmacology and the Study of Drugs

Naming Drugs

Sources of Drug Information

Sources of Drugs

Process for Drug Approval in the United States

Chemical Isolation and Identification

Animal Studies

Investigational New Drug Approval

Phase 1

Phase 2

Phase 3

New Drug Application

FDA New Drug Classification System

Orphan Drugs

The Prescription

Over-the-Counter Drugs

Generic Substitution in Prescriptions

Respiratory Care Pharmacology: An Overview

Aerosolized Agents Given by Inhalation

Related Drug Groups in Respiratory Care

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define pharmacology
2. Define drugs
3. Describe how drugs are named
4. List the various sources of drug information
5. List the various sources used to manufacture drugs
6. Describe the process for drug approval in the United States
7. Define orphan drugs
8. Differentiate between prescription drugs and over-the-counter (OTC) drugs
9. Apply the various abbreviations and symbols used in prescribing drugs
10. Describe the therapeutic purpose of each of the major aerosolized drug groups
11. Identify related drug groups in respiratory care

KEY TERMS AND DEFINITIONS

Acute respiratory distress syndrome (ARDS) Respiratory disorder characterized by respiratory insufficiency that may occur as a result of trauma, pneumonia, oxygen toxicity, gram-negative sepsis, and systemic inflammatory response.

Aerosolized agents Group of aerosol drugs for pulmonary applications that includes adrenergic, anticholinergic, mucoactive, corticosteroid, antiasthmatic, and antiinfective agents and surfactants instilled directly into the trachea.

Airway resistance (*Raw*) Measure of the impedance to ventilation caused by the movement of gas through the airway.

Brand name See Trade name.

Chemical name Name indicating the chemical structure of a drug.

Chronic obstructive pulmonary disease (COPD) Disease process characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lung to noxious particles or gases. Diseases that cause airflow limitation include chronic bronchitis, emphysema, asthma, and bronchiectasis.

Code name Name assigned by a manufacturer to an experimental chemical that shows potential as a drug. An example is aerosol SCH 1000, which was the code name for ipratropium bromide, a parasympatholytic bronchodilator (see [Chapter 7](#)).

Cystic fibrosis (CF) Inherited disease of the exocrine glands, affecting the pancreas, respiratory system, and apocrine glands. Symptoms usually begin in infancy and are

characterized by increased electrolytes in sweat, chronic respiratory infection, and pancreatic insufficiency.

Drug administration Method by which a drug is made available to the body.

Generic name Name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug.

Nonproprietary name Name of a drug other than its trademarked name.

Official name In the event that an experimental drug becomes fully approved for general use and is admitted to the *United States Pharmacopeia–National Formulary (USP-NF)*, the generic name becomes the official name.

Orphan drug Drug or biologic product for the diagnosis or treatment of a rare disease (affecting fewer than 200,000 persons in the United States).

Pharmacodynamics Mechanisms of drug action by which a drug molecule causes its effect in the body.

Pharmacogenetics Study of the interrelationship of genetic differences and drug effects.

Pharmacognosy Identification of sources of drugs, from plants and animals.

Pharmacokinetics Time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination.

Pharmacology Study of drugs (chemicals), including their origins, properties, and interactions with living organisms.

Pharmacy Preparation and dispensing of drugs.

***Pneumocystis jiroveci* (formerly *carinii*)** Organism causing *Pneumocystis* pneumonia in humans, seen in immunosuppressed individuals, such as those infected with human immunodeficiency virus (HIV).

Prescription Written order for a drug, along with any specific instructions for compounding, dispensing, and taking the drug. This order may be written by a physician, osteopath, dentist, veterinarian, and others but not by chiropractors or opticians.

Pseudomonas aeruginosa A gram-negative organism, primarily a nosocomial pathogen. It causes urinary tract infections, respiratory system infections, dermatitis, soft tissue infections, bacteremia, bone and joint infections, gastrointestinal infections, and various systemic infections, particularly in patients with severe burns and in patients who are immunosuppressed (e.g., patients with cancer or acquired immunodeficiency syndrome [AIDS]).

Respiratory care pharmacology Application of pharmacology to the treatment of pulmonary disorders and, more broadly, critical care. This chapter introduces and defines basic concepts and selected background information useful in the pharmacologic treatment of respiratory disease and critical care patients.

Respiratory syncytial virus (RSV) Virus that causes the formation of syncytial masses in cells. This leads to inflammation of the bronchioles, which may cause respiratory distress in young infants.

Therapeutics Art of treating disease with drugs.

Toxicology Study of toxic substances and their pharmacologic actions, including antidotes and poison control.

Trade name Brand name, or proprietary name, given to a drug by a particular manufacturer.

Pharmacology and the Study of Drugs

KEY POINT

Key terms in the study of pharmacology are introduced, including *drug* and *pharmacology*. The study of **respiratory care pharmacology** is broadly defined as the application of pharmacology to cardiopulmonary disease and critical care.

The many complex functions of the human organism are regulated by chemical agents. Chemicals interact with an organism to alter its function, providing methods of diagnosis, treatment, or prevention of disease. Such chemicals are termed *drugs*. A drug is any chemical that alters the organism's functions or processes. Examples include oxygen, alcohol, lysergic acid diethylamide (LSD), heparin, epinephrine, and vitamins. The study of drugs (chemicals), including their origins, properties, and interactions with living organisms, is the subject of **pharmacology**.

Pharmacology can be subdivided into the following more specialized topics:

Pharmacy: The preparation and dispensing of drugs

Pharmacognosy: The identification of sources of drugs, from plants and animals

Pharmacogenetics: The study of the interrelationship of genetic differences and drug effects

Therapeutics: The art of treating disease with drugs

Toxicology: The study of toxic substances and their pharmacologic actions, including antidotes and poison control

The principles of drug action from dose administration to effect and clearance from the body are the subject of processes known as **drug administration**, **pharmacokinetics**, and **pharmacodynamics**. These processes are defined and presented in detail in **Chapter 2**. **Table 1.1** summarizes key developments in the regulation of drugs in the United States.

Naming Drugs

KEY POINT

Each drug has five different names: chemical, code, official, generic, and trade (or brand). Sources of drug information include references, such as the *Physicians' Desk Reference (PDR)* and the *United States Pharmacopeia–National Formulary (USP-NF)*; textbooks, such as Goodman & Gilman's *The Pharmacological Basis of Therapeutics*; and subscription services, such as *Drug Facts and Comparisons* and *Clinical Pharmacology* by Gold Standard.

A manufacturer of a drug or pharmacologic agent must complete numerous steps set forth by the US Food and Drug Administration (FDA). Along the way, each agent picks up various labels rather than having a single name. An agent that becomes officially approved for general clinical use in the United States will have accumulated at least five different names, as follows:

Chemical name: The name indicating the drug's chemical structure.

Code name: A name assigned by a manufacturer to an experimental chemical that shows potential as a drug. An example is

TABLE 1.1 Legislation Affecting Drugs

1906	First <i>Food and Drugs Act</i> is passed by Congress; the <i>USP</i> and the <i>NF</i> were given official status.
1914	<i>Harrison Narcotic Act</i> is passed to control the importation, sale, and distribution of opium and its derivatives as well as other narcotic analgesics.
1938	<i>Food, Drug, and Cosmetic Act</i> becomes law. This is the current federal <i>Food, Drug, and Cosmetic Act</i> to protect the public health and to protect physicians from irresponsible drug manufacturers. This act is enforced by the FDA.
1952	<i>Durham-Humphrey Amendment</i> defines the drugs that may be sold by the pharmacist only on prescription.
1962	<i>Kefauver-Harris Amendment</i> is passed as an amendment to the <i>Food, Drug, and Cosmetic Act</i> of 1938. This law requires proof of the safety and efficacy of all drugs introduced since 1938. Drugs in use before that time have not been reviewed but are under study.
1970	<i>Controlled Substances Act</i> becomes effective; this act lists requirements for the control, sale, and dispensation of narcotics and dangerous drugs. Five schedules of controlled substances have been defined. Schedule I to Schedule V generally define drugs of decreasing potential for abuse, increasing medical use, and decreasing physical dependence. Examples of each schedule are as follows:
<i>Schedule I</i>	All nonresearch use is illegal; examples—heroin, marijuana, LSD, peyote, and mescaline.
<i>Schedule II</i>	No telephone prescriptions, no refills; examples—opium, morphine, certain barbiturates, amphetamines.
<i>Schedule III</i>	Prescription must be rewritten after 6 months or five refills; examples—certain opioid doses, anabolic steroids, and some barbiturates.
<i>Schedule IV</i>	Prescription must be rewritten after 6 months or five refills; penalties for illegal possession differ from those for Schedule III drugs; examples—phenobarbital, barbitol, chloral hydrate, meprobamate (Equanil, Miltown), and zolpidem (Ambien).
<i>Schedule V</i>	As for any nonopioid prescription drug; examples—narcotics containing non-narcotics in mixture form, such as cough preparations or Lomotil (diphenoxylate [narcotic; 2.5 mg] and atropine sulfate [nonnarcotic]).
1972	<i>Drug Listing Act</i> requires drug establishments that are engaged in the manufacturing, preparation, propagation, processing, or compounding of a drug to register their establishments and list all of their commercially marketed drug products with the FDA. This requirement includes establishments that repackage or change the container, labeling, or wrapper of any drug package in the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the customer.
1983	<i>Orphan Drug amendments</i> provided incentives for the development of drugs that treat diseases that affect fewer than 200,000 patients in the United States.
1984	<i>Drug Price Competition and Patent Restoration Act</i> provided abbreviated new drug application for generic medication. Allowed the patent to be extended for up to 5 years as a result of loss of marketing because of FDA reviews.
1992	<i>Prescription Drug User Fee Act</i> was reauthorized in 2007. User fees are paid for certain new drug applications by manufacturers.
1994	<i>Dietary Supplement Health and Education Act</i> established standards of dietary supplements. Specific ingredient and nutrition labels must be included on each package.
2002	<i>Bioterrorism Act</i> provided more stringent control on biologic agents and toxins.
2007	<i>FDA Amendments Act</i> gave the FDA greater authority over drug labeling, marketing, and advertising. Made clinical trial information more visible to the public.
2012	<i>FDA Safety and Innovation Act (FDASIA)</i> provided the FDA with power to collect fees (reauthorization from 2007), expedite agents of clinical significance, learn from patients first hand, and protect the global drug supply chain. All are efforts to make medications safer for US citizens.

For more information, access the FDA website at www.fda.gov.

FDA, Food and Drug Administration; LSD, lysergic acid diethylamide; NF, National Formulary; USP, United States Pharmacopeia.

aerosol SCH 1000, which was the code name for ipratropium bromide, a parasympatholytic bronchodilator (see [Chapter 7](#)).

Generic name: The name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug. Instead of a numeric or alphanumeric code, as in the code name, this name often is loosely based on the drug's chemical structure. For example, isoproterenol has an isopropyl group attached to the terminal nitrogen on the amino side chain, whereas metaproterenol is the same chemical structure as isoproterenol except that a dihydroxy attachment on the catechol nucleus is now in the so-called meta position (carbon-3,5 instead of carbon-3,4). The generic name is also known as the **nonproprietary name**, in contrast to the brand name.

Official name: If an experimental drug becomes fully approved for general use and is admitted to the *USP-NF*, the generic

name becomes the official name. Because an officially approved drug may be marketed by many manufacturers under different names, it is recommended that clinicians use the official name, which is nonproprietary, and not brand names.

Trade name: This is the **brand name**, or proprietary name, given by a manufacturer. For example, the generic drug named albuterol is currently marketed by Schering-Plough as Proventil-HFA, by GlaxoSmithKline as Ventolin-HFA, and by Teva as Proair HFA.

Following is an example of the various names for the drug zafirlukast, an agent intended to control asthma:

Chemical name: 4-(5-cyclopentyl-oxo-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide
Code name: ICI 204,219

Generic name: zafirlukast

Official name: zafirlukast

Trade (or brand) name: Accolate (AstraZeneca)

Sources of Drug Information

The *USP-NF* is a book of standards containing information about medications, dietary supplements, and medical devices. The FDA considers this book the official standard for drugs marketed in the United States.

Another source of drug information is the *Physicians' Desk Reference (PDR)*. Although prepared by manufacturers of drugs and potentially lacking the objectivity of the *USP-NF*, this annual volume provides useful information, including descriptive color charts for drug identification, names of manufacturers, and general drug actions.

The Drug Listing Act of 1972 requires registered drug establishments to provide the FDA with a current list of all drugs manufactured, propagated, prepared, processed, or compounded for commercial distribution. Drug products are identified and reported by using a unique, three-segment number, called the National Drug Code (NDC), which serves as a product identifier for drugs. If searching for specific product information on drugs used in the United States you may search the NDC database at <http://www.accessdata.fda.gov/scripts/cder/ndc/>.

A comprehensive and in-depth discussion of general pharmacologic principles and drug classes can be found in several texts. Two examples are the following (see References for a complete listing):

- Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, ed. 14¹
- *Basic and Clinical Pharmacology*, ed. 15²

An excellent way to obtain information on drug products and new releases is the monthly subscription service provided as *Drug Facts and Comparisons*, published by Facts & Comparisons.³

Sources of Drugs

Although the source of drugs is not a crucial area of expertise for the respiratory care clinician, it can be extremely interesting. Recognition of naturally occurring drugs dates to Egyptian papyrus records, to the ancient Chinese, and to the early Central American civilizations and is still recognized in remote regions of modern America, such as Appalachia.

For example, the prototype of cromolyn sodium was khellin, found in the eastern Mediterranean plant *Ammi visnaga*; this plant was used in ancient times as a muscle relaxant. Today, its synthetic derivative is used as an antiasthmatic agent. Another example is curare, derived from *Chondrodendron tomentosum* (a large vine) and used by South American Indians to coat their arrow tips for lethal effect. Its derivative is now used as a neuromuscular blocking agent. Digitalis is obtained from the foxglove plant (*Digitalis purpurea*) and was reputedly used by the Mayans for relief of angina. This cardiac glycoside is now used to treat heart conditions. The notorious poppy seed (*Papaver somniferum*) is the source of the opium alkaloids, immortalized in the book *Confessions of an English Opium-Eater*.⁴

Today, the most common source of drug preparation is chemical synthesis. Plants, minerals, and animals have often contributed to the synthesis of drug preparation. Examples of these sources include the following:

- *Animal*: thyroid hormone, insulin, pancreatic dornase
- *Plant*: Khellin (*Ammi visnaga*); atropine (belladonna alkaloid); digitalis (foxglove); reserpine (*Rauwolfia serpentina*); volatile oils of eucalyptus, pine, anise
- *Mineral*: copper sulfate, magnesium sulfate (Epsom salts), mineral oil (liquid hydrocarbons)

Process for Drug Approval in the United States

KEY POINT

The process of drug approval in the United States is lengthy and expensive and involves multiple phases.

The process by which a chemical moves from the status of a promising potential drug to one fully approved by the FDA for general clinical use is, on average, long, costly, and complex. Cost estimates vary, but in the 1980s, it took an average of 13 to 15 years from chemical synthesis to marketing approval by the FDA, with a cost of \$350 million in the United States.⁵ In a study done in 2003 by DiMasi et al.,⁶ it was calculated that companies spend over \$800 million on research and development and on preclinical and postclinical trials of a new drug. Adams and Brantner⁷ replicated DiMasi's calculations and estimated that companies spent over \$1 billion in 2010 to bring a new drug to market. DiMasi et al.⁸ have found that, today, pharmaceutical companies spend, on average, \$2.6 billion per drug to release a drug into the US market.

The major steps in the drug approval process have been reviewed by Flieger⁹ and by Hassall and Fredd.¹⁰ Box 1.1 outlines the major steps of the process.

Chemical Isolation and Identification

Because a drug is a chemical, the first step in drug development is to identify a chemical with the potential for useful physiologic effects. This step is exemplified by the plant product paclitaxel, which is derived from the needles and bark of the western yew tree (*Taxus brevifolia*). Paclitaxel showed antitumor activity, making it attractive for investigation as an anticancer drug. As the first step in the process of drug approval, the exact structure and physical

• BOX 1.1 Major Steps in the Process of Marketing a Drug in the United States

Isolation and Identification of the Chemical

Animal studies

General effects

Special effects on organ systems

Toxicology studies

Investigational New Drug Approval

Phase 1 studies: Small number, healthy subjects

Phase 2 studies: Small number, subjects with disease

Phase 3 studies: Large, multicenter studies

New Drug Application

Reporting system for first 6 months

and chemical characteristics of paclitaxel were established. Paclitaxel was subsequently developed and marketed as Taxol by Bristol-Myers Squibb.

Animal Studies

Once an active chemical is isolated and identified, a series of animal studies is performed to examine its general effect on the animal and effects on specific organs, such as the liver or kidneys. Toxicology studies to examine mutagenicity, teratogenicity, effect on reproductive fertility, and carcinogenicity are also performed.

Investigational New Drug Approval

At this point, an Investigational New Drug (IND) application is filed with the FDA for the chemical being examined. The IND application includes all the information previously gathered, as well as plans for human studies. These studies proceed in three phases and usually require about 3 years to complete.

Phase 1

The drug is investigated in a small group of healthy volunteers to establish its activity. This investigation is the basis for the pharmacokinetic description of the drug (rates of absorption, distribution, metabolism, and elimination).

Phase 2

The drug is then investigated as a treatment in a small number of individuals with the disease the drug is intended to treat.

Phase 3

The drug is investigated in large, multicenter studies to establish safety and efficacy.

New Drug Application

After a successful IND process, a New Drug Application (NDA) is filed with the FDA, and on approval, the drug is released for general clinical use. A detailed reporting system is in place for the first 6 months to track any problems that arise with the drug's use. The drug is no longer considered experimental (investigational) and can be prescribed for treatment of the general population by physicians.

The involved, lengthy, and expensive process of obtaining approval from the FDA to market a new drug in the United States has often been criticized. It may take up to 8 to 10 years for a drug to be tested and approved by the FDA.

FDA New Drug Classification System

Because some drugs are simply released in new forms or are like previously approved agents, the FDA has a classification system to help identify the significance of new products.¹¹ An alphanumeric code is given to provide this information (Box 1.2).

Orphan Drugs

KEY POINT

Certain drugs used for rare diseases, which may not return the cost of their development, are termed *orphan drugs*.

• BOX 1.2 Alphanumeric Coding System of the FDA

Chemical/Pharmaceutical Standing

- 1 = New chemical entity
- 2 = New salt form
- 3 = New dosage form
- 4 = New combination
- 5 = Generic drug
- 6 = New indication

Therapeutic Potential

- A = Important (significant) therapeutic gain over other drugs
- AA = Important therapeutic gain, indicated for a patient with AIDS; fast-track
- B = Modest therapeutic gain
- C = Important options; little or no therapeutic gain

AIDS, Acquired immunodeficiency syndrome; FDA, US Food and Drug Administration.

An **orphan drug** is a drug or biologic product used for the diagnosis or treatment of a rare disease. *Rare* is defined as a disease that affects fewer than 200,000 persons in the United States. Alternatively, a drug may be designated as an orphan if it is used for a disease that affects more than 200,000 persons but there is no reasonable expectation of recovering the cost of drug development. Table 1.2 lists several orphan drugs of interest to respiratory care clinicians.

The Prescription

KEY POINT

The selling of many drugs requires a health care prescriber's order, known as the *prescription*, and may involve Latin terms and abbreviations.

The **prescription** is the written order for a drug, along with any specific instructions for compounding, dispensing, and taking the drug. This order may be written by a physician, osteopath, dentist, veterinarian, and other health care practitioners, such as a physician assistant and nurse practitioner, but not by chiropractors or opticians. Today, although many prescriptions are written and distributed by electronic means, it is important to note that written prescriptions are still used. The detailed parts of a prescription are shown in Fig. 1.1. It should be noted that Latin and English, as well as metric and apothecary measures, are used for drug orders.

The directions (see 4 in Fig. 1.1) to the pharmacist for mixing or compounding drugs have become less necessary with the advent of the large pharmaceutical firms and their prepared drug products. The importance of these directions is in no way diminished, however, because misinterpretation is potentially lethal when dealing with drugs.

Since passage of the Controlled Substances Act of 1971, health care practitioners must include their registration number provided by the Drug Enforcement Administration (DEA) (usually termed a *DEA registration number*) when prescribing narcotics or controlled substances. Any licensed health care practitioner that has prescription rights may apply for a DEA registration number.

Table 1.3 lists the most common abbreviations seen in prescriptions.

TABLE 1.2 Examples of Orphan Drugs of Interest to Respiratory Care Clinicians

Drug	Proposed Use
Acetylcysteine	Intravenous administration for moderate to severe acetaminophen overdose
α_1 -Proteinase inhibitor (Prolastin)	Replacement therapy for congenital α_1 -proteinase (α_1 -antitrypsin) deficiency
Beractant (Survanta)	Prevention or treatment of RDS in newborns
CF transmembrane conductance regulator	Treatment of CF
Dornase alfa (Pulmozyme)	Treatment of CF: reduction of mucus viscosity and increase in airway secretion clearance
Nitric oxide gas (INOmax, GENOSYL)	Treatment of persistent pulmonary hypertension of newborns or of ARDS in adults
Tobramycin solution for inhalation (TOBI, Bethkis)	Treatment of <i>Pseudomonas aeruginosa</i> in CF or bronchiectasis
Pentamidine isethionate	Prevent <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia in high-risk patients

ARDS, Acute respiratory distress syndrome; CF, cystic fibrosis; RDS, respiratory distress syndrome.

Over-the-Counter Drugs

KEY POINT

An over-the-counter (OTC) drug does not require a prescription for purchase.

Many drugs are available to the general population without a prescription; these are referred to as *over-the-counter (OTC)* products. Although the strength and amount per dose may be less than that of a prescription formulation, OTC drugs can be hazardous, even in normal amounts, if their effects are not understood. In addition, when taken in large quantities, OTC products may increase risks to the consumer.

CLINICAL CONNECTION

For patients with mild asthma, racemic epinephrine is available over the counter (OTC) as an inhalation solution named Asthmanefrin. Racemic epinephrine can provoke cardiac arrhythmia or hypertension and can exacerbate these conditions if they preexist in a patient. Dependence on OTC preparations may encourage “self-treatment” that could mask or complicate a serious medical condition.

Generic Substitution in Prescriptions

A health care prescriber can indicate to the pharmacist that generic substitution is permitted in the filling of a prescription. In such a case, the pharmacist may provide any manufacturer's version of the prescribed drug and not a specific brand. This practice is intended to save money because the manufacturer of the generic substitute has not invested considerable time and money in developing the

• **Fig. 1.1** Parts of a prescription. 1. Patient's name and address and the date the prescription was written. 2. **R** (meaning “recipe” or “take thou”) directs the pharmacist to take the drug listed and prepare the medication. This is referred to as the *superscription*. 3. The inscription lists the name and quantity of the drug being prescribed. 4. When applicable, the health care prescriber includes a subscription, which provides directions to the pharmacist on how to prepare the medication. For example, a direction to make an ointment, which might be appropriate for certain medications, would be “ft ung.” In many cases, with precompounded drugs, counting out the correct number is the only requirement. 5. *Sig* (*signa*) means “write.” The transcription or signature is the information the pharmacist writes on the label of the medication as instructions to the patient. 6. Name of the prescriber: Although the health care prescriber signs the prescription, the word “signature,” as described in Part 5, denotes the directions to the patient, not the prescriber's name.

original drug product, and presumably the generic substitute is less expensive to the consumer compared with the original proprietary brand.

Respiratory Care Pharmacology: An Overview

KEY POINT

Aerosolized agents are central to respiratory care in pulmonary diseases. This group of drugs includes adrenergic, anticholinergic, mucoactive, corticosteroid, antiasthmatic, and antiinfective agents and surfactants instilled directly into the trachea. Other drug groups important in respiratory care include cardiovascular, antiinfective, neuromuscular-blocking, and diuretic agents.

Helping people with pulmonary diseases, such as **cystic fibrosis (CF)**, or pulmonary derangement such as **acute respiratory distress syndrome (ARDS)**, defines a spectrum of pharmacologic care from maintenance support of a person with stable disease through intervention for a critically ill patient. The respiratory system cannot be dissociated from the cardiac and vascular systems, given the interlinked function of these systems. As a result, respiratory care pharmacology involves a relatively broad area of drug classes.

**TABLE
1.3****Abbreviations and Symbols Used in Prescriptions***

Abbreviation	Meaning	Abbreviation	Meaning
ā	before	ol	oil
āā	of each	OS	left eye
ac	before a meal	OU	both eyes
ad lib	as much as desired	̄P	after
alt hor	every other hour	part aeq	equal parts
aq dest	distilled water	pc	after meals
bid	twice daily	pil	pill
C, cong	gallon	placebo	I please (inert substitute)
ċ	with	po	per os (by mouth)
cap	capsule	prn	as needed
cc	cubic centimeter (another term for milliliter [mL])	pr	rectally
dil	dilute	pulv	powder
dtd	give such doses	q	every
elix	elixir	qh	every hour
emuls	emulsion	qid	four times daily
et	and	qod	every other day
ex aq	in water	qd	every day
ext	extract	q2h	every 2 hours
fld	fluid	q3h	every 3 hours
ft	make	q4h	every 4 hours
gel	a gel, jelly	qs	as much as required (quantity sufficient)
g	gram	qt	quart
gr	grain	Rx, R	take
gtt	a drop	̄S	without
hs	at bedtime	sig	write
IM	intramuscular	sol	solution
IV	intravenous	solv	dissolve
L	liter	sos	if needed (for one time)
lin	liniment	spt	spirit
liq	liquid, solution	sp frumenti	whiskey
lot	lotion	̄S̄	half
M	mix	stat	immediately
mist, mixt	mixture	syr	syrup
mL	milliliter	tab	tablet or tablets
nebul	a spray	tid	three times daily
non rep	not to be repeated	tr, tinct	tincture
npo	nothing by mouth	ung	ointment
O, ̄o	pint	ut dict	as directed
OD	right eye	vin	wine

*Not all of these abbreviations are considered safe practice; however, they may still be seen occasionally.

Aerosolized Agents Given by Inhalation

Drugs delivered by oral inhalation or nasal inhalation are intended to provide a local topical treatment of the respiratory tract. The following are advantages of this method and route of delivery:

- Aerosol doses are smaller than doses used for the same purpose and given systemically.
- Side effects are usually fewer and less severe with aerosol delivery than with oral or parenteral delivery.

- The onset of action is rapid.
- Drug delivery is targeted to the respiratory system, with lower systemic bioavailability.
- The inhalation of aerosol drugs is painless, relatively safe, and may be convenient, depending on the specific delivery device used.

The classes of aerosolized agents (including surfactants, which are directly instilled into the trachea), their uses, and individual agents are summarized in [Table 1.4](#).

TABLE 1.4 Common Agents Used in Respiratory Therapy

Drug Group	Therapeutic Purpose	Agents
Adrenergic agents	<i>β-Adrenergic:</i> Relaxation of bronchial smooth muscle and bronchodilation, to reduce airway resistance (R_{aw}) and to improve ventilatory flow rates in airway obstruction resulting from chronic obstructive pulmonary disease (COPD) , asthma, CF, acute bronchitis	Albuterol Arformoterol Formoterol Indacaterol Levalbuterol Metaproterenol Olodaterol Salmeterol Vilanterol
	<i>α-Adrenergic:</i> Topical vasoconstriction and decongestion Used to treat upper airway swelling	Racemic epinephrine
Anticholinergic agents	Relaxation of cholinergically induced bronchoconstriction to improve ventilatory flow rates in COPD and asthma	Acclidinium bromide Glycopyrrolate bromide Ipratropium bromide Tiotropium bromide Umeclidinium bromide
Mucoactive agents	Modification of properties of respiratory tract mucus; current agents reduce viscosity and promote clearance of secretions	Acetylcysteine Dornase alfa Hyperosmolar saline Mannitol
Corticosteroids	Reduction and control of airway inflammatory response usually associated with asthma (lower respiratory tract) or with seasonal or chronic rhinitis (upper respiratory tract)	Beclomethasone dipropionate Budesonide Ciclesonide Flunisolide Fluticasone furoate Fluticasone propionate Mometasone furoate
Antiasthmatic agents	Prevention of onset and development of the asthmatic response through inhibition of chemical mediators of inflammation	Cromolyn sodium Benralizumab Mepolizumab Montelukast Omalizumab Relizumab Zafirlukast Zileuton
Antiinfective agents	Inhibition or eradication of specific infective agents, such as <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) (pentamidine), respiratory syncytial virus (RSV) (ribavirin), <i>Pseudomonas aeruginosa</i> in CF or influenza A and B	Aztreonam Pentamidine Ribavirin Tobramycin Zanamivir
Exogenous surfactants	Approved clinical use is by direct intratracheal instillation for the purpose of restoring more normal lung compliance in RDS of newborns	Beractant Calfactant Lucinactant Poractant alfa
Prostacyclin analogs	Clinically indicated to treat pulmonary hypertension for the purpose of decreasing shortness of breath and increasing walking distance	Iloprost Treprostinil

CF, Cystic fibrosis; RDS, respiratory distress syndrome.

Related Drug Groups in Respiratory Care

Additional groups of drugs important in critical care are the following:

- *Antiinfective agents*, such as antibiotics or antituberculous drugs
- *Neuromuscular blocking agents*, such as curariform agents and others
- *Central nervous system agents*, such as analgesics and sedatives/hypnotics
- *Antiarrhythmic agents*, such as cardiac glycosides and lidocaine
- *Antihypertensive and antianginal agents*, such as β -blocking agents or nitroglycerin
- *Anticoagulant and thrombolytic agents*, such as heparin or streptokinase
- *Diuretics*, such as the thiazides or furosemide

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What is the definition of the term *drug*?
2. What is the difference between the generic name and trade name of a drug?
3. What part of a prescription contains the name and amount of the drug being prescribed?
4. A physician's order reads as follows: "gtt iv of racemic epinephrine, $\bar{c}$ 3 cc of normal saline, q4h, while awake." What has been ordered?
5. The drug salmeterol was released for general clinical use in the United States in 1994. Where would you look to find information about this drug, such as the available dosage forms, doses, properties, side effects, and action?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 24-year-old man played golf on a newly mown course. He had exhibited allergies in the past few years and was diagnosed as having asthma. He did not have a regular physician or medical treatment site, and he was not taking any medications to control his asthma and allergies. He began to experience difficulty breathing later in the day, with wheezing and

some shortness of breath on mild exertion. He visited his local drugstore and purchased Primatene Mist. On use, he obtained immediate relief for his breathing, but his heart rate increased from 66 beats/min to 84 beats/min, and he felt shaky. By midnight, his wheezing had returned. He continued using the Primatene Mist through the next morning. The relief he experienced with use of the drug diminished during the afternoon, and a friend found him later that evening with audible wheezing, gasping for air, and in severe respiratory distress. The patient was rushed to a local emergency department, where he went into respiratory arrest approximately 5 minutes after arrival.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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2

Principles of Drug Action

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Drug Administration Phase

Drug Dosage Forms

Drug Formulations and Additives

Routes of Administration

Enteral

Parenteral (Injectable)

Transdermal

Inhalation

Topical

Pharmacokinetic Phase

Absorption

Aqueous Diffusion

Lipid Diffusion

Carrier-Mediated Transport

Pinocytosis

Factors Affecting Absorption

Distribution

Volume of Distribution

Metabolism

Site of Drug Biotransformation

Enzyme Induction and Inhibition

First-Pass Effect

Elimination

Plasma Clearance

Maintenance Dose

Plasma Half-Life

Time–Plasma Curves

Pharmacokinetics of Inhaled Aerosol Drugs

Local Versus Systemic Effect

Inhaled Aerosols in Pulmonary Disease

Distribution of Inhaled Aerosols

Lung Availability/Total Systemic Availability Ratio

Pharmacodynamic Phase

Structure–Activity Relationships

Nature and Type of Drug Receptors

Drug Receptors

Lipid-Soluble Drugs and Intracellular Receptor Activation

Drug-Regulated Ion Channels

Receptors Linked to G Proteins

Dose–Response Relationships

Potency Versus Maximal Effect

Therapeutic Index

Agonists and Antagonists

Drug Interactions

Terms for Drug Responsiveness

Pharmacogenetics

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to principles of drug action
2. Define drug administration phase
3. Describe the various routes of administration available
4. Define pharmacokinetic phase
5. Discuss the key factors in the pharmacokinetic phase (e.g., absorption, distribution, metabolism, and elimination)
6. Describe the first-pass effect
7. Differentiate between systemic and inhaled drugs in relation to the pharmacokinetic phase
8. Explain the lung availability/total systemic availability (L/T) ratio
9. Define pharmacodynamic phase
10. Discuss the importance of structure–activity relationships
11. Discuss the role of drug receptors
12. Discuss the importance of dose–response relationships
13. Describe the importance of pharmacogenetics

KEY TERMS AND DEFINITIONS

Agonist Chemical or drug that binds to a receptor and creates an effect on the body.

Antagonist Chemical or drug that binds to a receptor but does not create an effect on the body; it blocks the receptor site from accepting an agonist.

Bioavailability Amount of drug that reaches the systemic circulation.

Drug administration Method by which a drug is made available to the body.

Enteral Use of the intestine.

First-pass effect Initial metabolism in the liver of a drug taken orally before the drug reaches the systemic circulation.

Hypersensitivity Allergic or immune-mediated reaction to a drug, which can be serious, requiring airway maintenance or ventilatory assistance.

Idiosyncratic effect Abnormal or unexpected reaction to a drug, other than an allergic reaction, compared with the predicted effect.

Inhalation Taking a substance, typically in the form of gases, fumes, vapors, mists, aerosols, or dusts, into the body by breathing in.

Local effect Limited to the area of treatment (e.g., inhaled drug to treat constricted airways).

Lung availability/total systemic availability ratio (L/T ratio) Amount of drug that is made available to the lung out of the total available to the body.

Parenteral Administration of a substance in any way other than the intestine, most commonly an injection (e.g., intravenous, intramuscular, subcutaneous, intrathecal, or intraosseous).

Pharmacodynamics Mechanisms of drug action by which a drug molecule causes its effect in the body.

Pharmacogenetics Study of genetic factors and their influence on drug response.

Pharmacokinetics Time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination.

Receptor Cell component that combines with a drug to change or enhance the function of the cell. Structure–activity relationship (SAR) Relationship between a drug's chemical structure and the outcome it has on the body.

Synergism Drug interaction that occurs from two or more drug effects that are greater than if the drugs were given alone.

Systemic effect Pertains to the whole body, whereas the target for the drug is not local, possibly causing side effects (e.g., capsule of acetaminophen for a headache).

Tachyphylaxis Rapid decrease in response to a drug.

Therapeutic index (TI) Difference between the minimal therapeutic and toxic concentrations of a drug; the smaller the difference, the greater the risk the drug will be toxic.

Tolerance Decreasing intensity of response to a drug over time.

Topical Use of the skin or mucous membrane (e.g., lotion).

Transdermal Use of the skin (e.g., patch).

The entire course of action of a drug, from dose to effect, can be understood in three phases: the drug administration, pharmacokinetic, and pharmacodynamic phases. This useful conceptual framework, based on the principles offered by Holford,¹ organizes the steps of a drug's action from **drug administration** (method by which a drug dose is made available to the body) through effect and ultimate elimination from the body. This framework is illustrated in Fig. 2.1, which provides an overview of the interrelationship of the three phases of drug action, each of which is discussed in this chapter.

KEY POINT

Principles of drug action encompass three major topic areas: drug administration, pharmacokinetics, and pharmacodynamics.

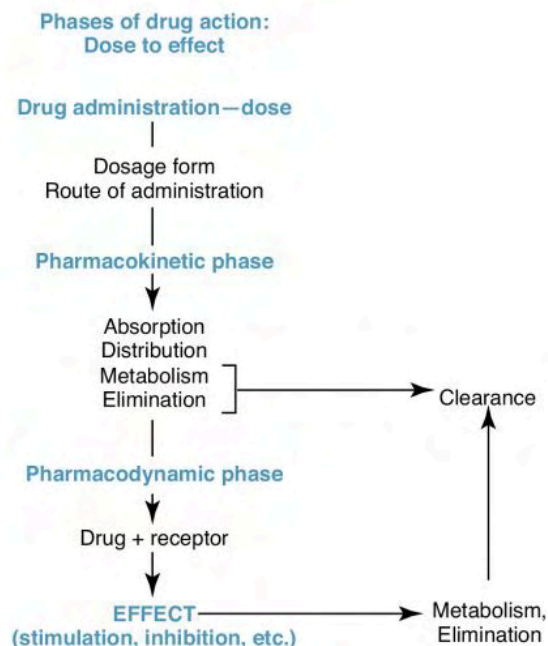
Drug Administration Phase

KEY POINT

The *drug administration* phase identifies drug dosage forms and routes of administration. The *pharmacokinetic phase* describes the factors determining drug absorption, distribution in the body, metabolism, breakdown of the active drug to its metabolites, and elimination of the active drug and inactive metabolites from the body.

Drug Dosage Forms

The drug administration phase entails the interrelated concepts of drug formulation (e.g., compounding a tablet for particular



• **Fig. 2.1** Conceptual scheme illustrating the major phases of drug action in sequence, from dose administration to effect in the body. (From Katzung, B.G., Masters, S.B., & Trevor, A.J. [Eds.] [2012]. *Basic and Clinical Pharmacology* [12th ed.]. New York: McGraw Hill Medical.)

dissolution properties) and drug delivery (e.g., designing an inhaler to deliver a unit dose). Two key topics of this phase are the drug dosage form and the route of administration. The *drug dosage form* is the physical state of the drug in association with nondrug components. Tablets, capsules, and injectable solutions are common drug dosage forms. The *route of administration* is the portal of entry for the drug into the body, such as oral (enteral), injection, or inhalation. The form in which a drug is available must be compatible with the route of administration preferred. The injectable route (e.g., intravenous route) requires a liquid solution of a drug, whereas the oral route can accommodate capsules, tablets, or liquid solutions. Some common drug formulations for each of the common routes of drug administration are listed in Table 2.1.

Drug Formulations and Additives

A drug is the active ingredient in a dosage formulation, but it is usually not the only ingredient in the total formulation. For example, in a capsule of an antibiotic, the capsule itself is a gelatinous material that allows for swallowing of the drug. The capsule material disintegrates in the stomach, and the active drug ingredient is released for absorption. The rate at which the active drug is liberated from a capsule or tablet can be controlled during the formulation process by altering drug particle size or by using a specialized coating or formulation matrix. Aerosolized agents for inhalation and treatment of the respiratory tract also contain ingredients other than the active drug, such as preservatives, propellants for metered dose inhaler (MDI) formulations, dispersants (surfactants), and carrier agents for dry powder inhalers (DPIs). Table 2.2 presents the various formulations with different ingredients for the beta (β)-adrenergic bronchodilator albuterol. In the nebulizer solution, benzalkonium chloride is a preservative, and

sulfuric acid adjusts the pH of the solution. In the hydrofluoroalkane (HFA)-MDI, a hydrofluoroalkane is used as a propellant.

Routes of Administration

Advances in drug formulation and delivery systems have yielded a wide range of routes by which a drug can be administered. In the following discussion, routes of administration have been divided into five broad categories: enteral, parenteral, transdermal, inhalation, and topical.

Enteral

The term **enteral** refers literally to the small intestine, but the enteral route of administration is more broadly applicable to administration of drugs intended for absorption anywhere along the gastrointestinal tract. The most common enteral route is by mouth (oral) because it is convenient, is painless, and offers flexibility in possible dosage forms of the drug, as shown in Table 2.1. The oral route requires the patient to be able to swallow; therefore airway-protective reflexes should be intact. If the drug is not destroyed or inactivated in the stomach and can be absorbed into the bloodstream, distribution throughout the body and a **systemic effect** can be achieved. Other enteral routes of administration include suppositories inserted in the rectum, tablets placed under the tongue (sublingual), and drug solutions introduced through an indwelling gastric tube.

Parenteral (Injectable)

Technically, the term **parenteral** means “besides the intestine,” which implies any route of administration other than enteral. However, the parenteral route commonly refers to injection of a drug. Various options are available for injection of a drug, the most common of which are the following:

- **Intravenous (IV)**: Injected directly into the vein, allowing nearly instantaneous access to systemic circulation. Drugs can be given as a bolus, in which case the entire dose is given rapidly, leading to a sharp increase in the drug's plasma concentration, or a steady infusion can be used to avoid this precipitous increase.
- **Intramuscular (IM)**: Injected deep into a skeletal muscle. Because the drug must be absorbed from the muscle into the systemic circulation, the drug effects occur more gradually than with intravenous injection, although typically more rapidly than by the oral route.
- **Subcutaneous (SC)**: Injected into the subcutaneous tissue beneath the epidermis and the dermis.
- **Intrathecal (IT)**: Injected into the arachnoid membrane of the spinal cord to diffuse throughout the spinal fluid.
- **Intraosseous (IO)**: Injected into the marrow of the bone.

Transdermal

An increasing number of drugs are being formulated for application to the skin (i.e., **transdermal** administration) to produce a systemic effect. The advantage of this route is that it can supply long-term continuous delivery to the systemic circulation. The drug is absorbed percutaneously, obviating the need for a hypodermic needle and decreasing the fluctuations in plasma drug levels that can occur with repeated oral administration.

Inhalation

Drugs can be given by **inhalation** for either a systemic effect or a local effect in the lung. Two of the most common drug

TABLE 2.1 Common Drug Formulations for Various Routes of Administration

Enteral	Parenteral	Inhalation	Transdermal	Topical
Tablet	Solution	Gas	Patch	Powder
Capsule	Suspension	Aerosol	Paste	Lotion
Suppository	Depot	—	—	Ointment
Elixir	—	—	—	Solution
Suspension	—	—	—	—

TABLE 2.2 Three Different Dosage Forms for the Bronchodilator Drug Albuterol, Indicating Ingredients Other Than Active Drug

Dosage Form	Active Drug	Ingredients
Nebulizer solution	Albuterol sulfate	Benzalkonium chloride, sulfuric acid
Respimat	Albuterol- ipratropium	Benzalkonium chloride, edetate disodium hydrochloric acid
Tablets	Albuterol sulfate	Lactose, butylparaben, sugar
MDI-HFA	Albuterol	1,1,1,2-Tetrafluoroethane, ethanol, oleic acid

HFA, Hydrofluoroalkane; MDI, metered dose inhaler.

formulations given by this route are gases, which usually are given by inhalation for anesthesia (a systemic effect), and aerosolized agents intended to target the lung or respiratory tract in the treatment of respiratory disease (**local effect**). The technology and science of aerosol drug delivery to the respiratory tract continue to develop and are described in detail in [Chapter 3, Box 2.1](#) provides a summary of devices commonly used for inhaled aerosol drug delivery. The general rationale for aerosolized drug delivery to the airways for treating respiratory disease is the local delivery of the drug to the target organ, with reduced or minimal body exposure to the drug and, it is hoped, reduced prevalence or severity of possible side effects.

Topical

Drugs can be applied directly to the skin or mucous membranes to produce a local effect. Such drugs are often formulated to minimize systemic absorption. Examples of **topical** administration include the application of corticosteroid cream to an area of contact dermatitis (e.g., poison ivy rash), administration of an eye drop containing a β -adrenergic antagonist to control glaucoma, and instillation of nasal drops containing an α -adrenergic agonist to relieve congestion.

Pharmacokinetic Phase

The term pharmacokinetic phase refers to the time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination. Once presented to the body, as described in the drug administration phase, a drug crosses local anatomic barriers to varying extents, depending on its chemical properties and the physiologic environment of the body compartment it occupies. For a systemic effect, it is desirable for the drug to get into the bloodstream for distribution throughout the body; for a local effect, this is not desirable and can lead to unwanted side effects throughout the body. Absorption, distribution, metabolism, and elimination are the factors influencing and determining the course of a drug after it is introduced to the body. In essence, **pharmacokinetics** describes what the body does to a drug, and **pharmacodynamics** describes what the drug does to the body.

Absorption

When given orally for a systemic effect, a pill must first dissolve to liberate the active ingredient. The free drug must then reach the epithelial lining of the stomach or intestine and traverse the lipid membrane barriers of the gastric and vascular cells before reaching the bloodstream for distribution throughout the body. The lining of the lower respiratory tract also presents barriers to

drug absorption. This mucosal barrier consists of five identifiable elements:

1. Airway surface liquid
2. Epithelial cells
3. Basement membrane
4. Interstitium
5. Capillary vascular network

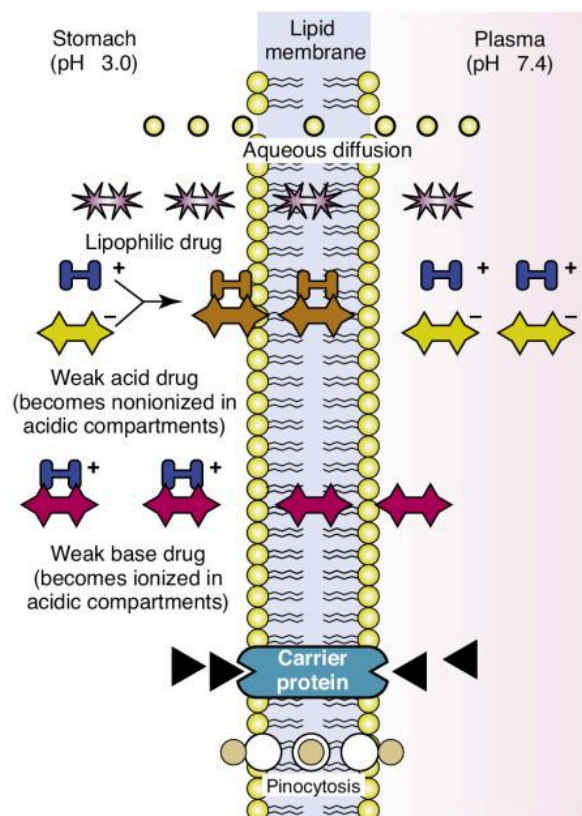
After traversing these layers, a drug can reach the smooth muscle or glands of the airway. The mechanisms by which drugs move across membrane barriers include aqueous diffusion, lipid diffusion, active or facilitated diffusion, and pinocytosis. Generally, a drug must be sufficiently water soluble to reach a lipid (cell) membrane and sufficiently lipid soluble to diffuse across the cell barrier. [Fig. 2.2](#) illustrates these basic mechanisms.

Aqueous Diffusion

Aqueous diffusion occurs in the aqueous compartments of the body, such as the interstitial spaces or the space within a cell. Transport across epithelial linings is restricted because of small pore size; capillaries have larger pores, allowing passage of most drug molecules. Diffusion occurs by a concentration gradient.

Lipid Diffusion

Lipid diffusion is an important mechanism for drug absorption because of the many epithelial membranes that must be crossed if a drug is to distribute in the body and reach its target organ. Epithelial cells have lipid membranes, and a drug must be lipid



• **Fig. 2.2** Pathways by which drugs can traverse lipid membranes and enter the circulation. A membrane separating an acidic compartment (stomach) and a neutral compartment (plasma) is shown to illustrate that only the nonionized forms of weak acids or weak bases cross these lipophilic barriers more readily than ionized forms.

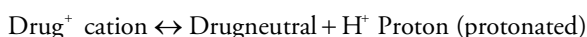
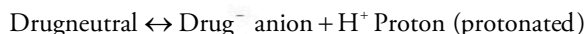
• BOX 2.1 Devices for Inhaled Administration of Drugs

- Vaporizer (anesthetic gases)
- Atomizer
- Nebulizer, small or large
- Metered dose inhaler (MDI), with or without spacer
- Respimat soft mist inhaler
- Dry powder inhaler (DPI)
- Ultrasonic nebulizer (USN)

soluble (nonionized, nonpolar) to diffuse across such a membrane. Lipid-insoluble drugs tend to be ionized, that is, have positive and negative charges separated on the molecule (polar), and are water soluble.

Many drugs are weak acids or weak bases, and the degree of ionization of these molecules is dependent on the pK_a (the pH at which the drug is 50% ionized and 50% nonionized), the ambient pH, and whether the drug is a weak acid or base. The direction of increasing ionization is opposite for weak acids and weak bases while the ambient pH changes.

Weak acid: Because an acid contributes protons (H^+ ions), the protonated form is neutral, or nonionized.



Weak base: Because a base accepts protons (hydrogen [H^+] ions), the unprotonated form is neutral, or nonionized.

- The protonated weak acid is neutralized by the addition of H^+ ions in an acidic environment, is nonionized, and is lipid soluble.
- The protonated weak base gains a charge by adding H^+ ions in an acidic environment, is ionized, and is not lipid soluble.

Fig. 2.2 conceptually illustrates the principle of lipid diffusion and absorption for weak acids and bases.

Some drugs, such as ethanol, are neutral molecules and are always nonionized. They are well absorbed into the bloodstream and across the blood–brain barrier. Other drugs, such as ipratropium bromide and *d*-(+)-tubocurarine, are quaternary amines, have no unshared electrons for reversible binding of H^+ ions, and are permanently positively charged. Ipratropium is not lipid soluble and does not absorb and distribute well from the mouth or the lung with oral inhalation. A secondary or tertiary amine, such as atropine, can give up its H^+ ion and become nonionized, increasing its absorption, distribution, and consequent side effects in the body.

Carrier-Mediated Transport

Special carrier molecules embedded in the lipid membrane can transport some substances, such as amino acids, sugars, or naturally occurring peptides, and the drugs that resemble these substances. In some instances, a drug can compete with the endogenous substance normally transported by the carrier.

Pinocytosis

Pinocytosis refers to the incorporation of a substance into a cell by a process of membrane engulfment and transport of the substance within vesicles, allowing translocation across a membrane barrier.

Factors Affecting Absorption

The route of administration determines which barriers to absorption must be crossed by a drug. These barriers can affect the drug's time to onset and time to peak effect. Intravenous administration bypasses the need for absorption from the gastrointestinal tract seen with oral administration, generally gives a very rapid onset and peak effect, and provides 100% availability of the drug in the bloodstream. The term **bioavailability** indicates the proportion of a drug that reaches the systemic circulation. For example, the bioavailability of oral morphine is 0.24 because only about a quarter of the morphine ingested actually arrives in the systemic circulation.

Bioavailability is influenced not only by absorption but also by inactivation caused by stomach acids and by metabolic degradation, which can occur before the drug reaches the main systemic compartment. Another important variable governing absorption and bioavailability is blood flow to the site of absorption.

Distribution

To be effective at its desired site of action, a drug must have a certain concentration. An antibiotic is investigated for its *minimal inhibitory concentration (MIC)*—the lowest concentration of a drug at which a microbial population is inhibited. *Drug distribution* is the process by which a drug is transported to its sites of action, is eliminated, or is stored. When given intravenously, most drugs distribute initially to organs that receive the most blood flow. After this brief initial distribution phase, subsequent phases of distribution occur on the basis of the principles of diffusion and transport outlined earlier and the drug's physical and chemical nature and ability to bind to plasma proteins. The initial distribution phase is clinically important for lipophilic anesthetics (e.g., propofol and thiopental) because they produce rapid onset of anesthesia as a function of the high blood flow to the brain, and their effects are quickly terminated during redistribution to other tissues. The binding of drugs to plasma proteins can also be clinically relevant in rare instances, such as when a large portion of a drug is inactive because it is bound to plasma proteins but subsequently becomes displaced (and, thus, active) by a second drug that binds to the same proteins.

The plasma concentration of a drug is partially determined by the rate and extent of absorption versus the rate of elimination for a given dose amount. The volume of the compartment in which the drug is distributed also determines the concentration achieved in plasma. Compartments and their approximate volumes in a 70-kg adult are given in Table 2.3.

Volume of Distribution

Suppose a certain drug that distributes exclusively in the plasma compartment is administered intravenously. If a 10-mg bolus of the drug is given, and the volume of the patient's plasma compartment is 5 L, the concentration in the plasma (barring degradation or elimination) would be 2 mg/L. In this simple example, the *volume of distribution* (V_D) is the same as the volume of the plasma compartment. In practice, drug distribution is usually more complex, and the actual tissue compartments occupied by the drug are unknown. Nonetheless, V_D describes a useful mathematical equation relating the total amount of drug in the body to the plasma concentration:

$$\text{Volume of distribution } (V_D) = \frac{\text{Drug amount}}{\text{Plasma concentration}}$$

TABLE 2.3 Volumes (Approximate) of Major Body Compartments

Compartment	Volume (L)
Vascular (blood)	5
Interstitial fluid	10
Intracellular fluid	20
Fat (adipose tissue)	14–25

Example

If 350 mg of theophylline results in a concentration in the plasma of 10 mg/L (equivalent to 10 mcg/mL), the volume of distribution (V_D) is calculated as:

$$V_D = \frac{350 \text{ mg}}{10 \text{ mg/L}}$$

$$V_D = 35 \text{ L}$$

The drug can be absorbed and distributed into sites other than the vascular compartment, which is only approximately 5 L, and the calculated volume of distribution can be much larger than the blood volume, as in the case of theophylline, which has a V_D of 35 L in a 70-kg adult. For this reason, V_D is referred to as the *apparent volume of distribution* to emphasize that V_D does not refer to an actual physiologic space. Some drugs, such as fluoxetine (an antidepressant) and inhaled anesthetics, are sequestered in peripheral tissues and can have apparent volumes of distribution many times greater than the entire volume of the body.

In a clinical setting, V_D is rarely measured but is, nonetheless, important for estimating the dose needed to achieve a given therapeutic level of a drug. By rearranging the equation for V_D , the drug amount should equal the V_D multiplied by the concentration.

Example

To achieve a theophylline concentration of 15 mg/L with a V_D of 35 L, we calculate a dose of:

$$\text{Drug amount (drug dose)} = \text{Plasma concentration} \times V_D$$

$$\text{Dose} = 15 \text{ mg/L} \times 35 \text{ L}$$

$$\text{Dose} = 525 \text{ mg}$$

The following points should be noted:

- The preceding calculation assumes that the dose is completely available to the body. This may be true if a dose is given intravenously, but there may be less than 100% bioavailability if a dose is given orally.
- This is a *loading dose*, and subsequent doses to maintain a level of concentration depend on the rate of absorption versus the rates of metabolism and excretion (discussed in the next sections).
- V_D may change as a function of age or disease state.
- The concept of V_D is not directly helpful in topical drug administration and delivery of aerosolized drugs intended to act directly on the airway surface. V_D for topical deposition in the airway is not measured, and the drug is deposited locally in the respiratory tract, and some drugs are absorbed from the airway into blood.

Metabolism

KEY POINT

The liver is a primary site of drug metabolism and biotransformation, and the kidneys are the primary site of drug excretion, although both drugs and metabolites can also be excreted in feces.

The processes by which drug molecules are metabolized, or biotransformed, constitute a complex area of biochemistry that is beyond the scope of this text. Common pathways for the biotransformation of drugs are listed in [Box 2.2](#). Generally, phase 1 biochemical reactions convert the active drug to a more polar (water-soluble) form, which can be excreted by the kidney. Drugs that are transformed in a phase 1 reaction may be transformed further in a phase 2 reaction, which combines (conjugates) a substance (e.g., glucuronic acid) with the metabolite to form a highly polar conjugate. In the case of some drugs, biotransformation is accomplished by just phase 1 or phase 2 metabolism without prior transformation by the other phase. Metabolites are often less biologically active than the parent drug. Nevertheless, some drugs are inactive until metabolized (e.g., enalapril) or produce metabolites that are more toxic than their progenitors (e.g., breakdown products of acetaminophen).

Site of Drug Biotransformation

The liver is the principal organ for drug metabolism, although other tissues, including the lung, intestinal wall, and endothelial vascular wall, can transform or metabolize drugs. For example, epinephrine, a weak base, is absorbed into the intestinal wall, where sulfatase enzymes inactivate it as the drug diffuses into the circulation. The liver contains intracellular enzymes that usually convert lipophilic (lipid-soluble) drug molecules into water-soluble metabolites that are more easily excreted. The major enzyme system in the liver is the cytochrome P450 oxidase system (CYP). There are many forms of cytochrome P450, which are hemoproteins with considerable substrate versatility and the ability to metabolize new drugs or industrial compounds. The various forms of cytochrome P450 have been divided into about a dozen subcategories, termed *isoenzyme families*. The four most important isoenzyme families for drug metabolism have been designated *CYP1*, *CYP2*, *CYP3*, and *CYP4*. A given drug may be metabolized predominantly by only one member of an isoenzyme family, whereas another drug may be metabolized by multiple enzymes in the same family or by several distinct enzymes across families. Knowing which particular CYP enzyme metabolizes a drug may be important for predicting drug interactions, as further described subsequently.

Enzyme Induction and Inhibition

Chronic administration or abuse of drugs that are metabolized by the enzyme systems in the liver can induce (increase) or inhibit the levels of the enzymes (enzyme induction and inhibition). Examples of drugs or agents that can induce or inhibit CYP enzymes are listed in [Table 2.4](#).

• BOX 2.2 Common Pathways for Drug Metabolism

Phase 1

- Oxidative hydroxylation
- Oxidative dealkylation
- Oxidative deamination
- N-oxidation
- Reductive reactions
- Hydrolytic reactions (e.g., esterase enzymes)

Phase 2

- Conjugation reactions (e.g., glucuronide or sulfate)

Enzyme induction can affect the therapeutic doses of drugs required. Rifampin can induce CYP enzymes and increase the metabolism of several drugs, including warfarin and oral contraceptives. Likewise, cigarette smoking can increase the breakdown of theophylline in patients with chronic lung disease, shortening the half-life of the drug from approximately 7.0 to 4.3 hours. Dosages would need to be adjusted accordingly to maintain a suitable plasma level of theophylline. Conversely, a substantial portion of drug interactions involves inhibition of CYP enzymes. A given drug is not likely to inhibit all the CYP isoenzymes equally. For example, the antibiotic ciprofloxacin is a potent inhibitor of an enzyme in the CYP family that also metabolizes theophylline. Coadministration of ciprofloxacin with theophylline can increase theophylline levels—the opposite effect of cigarette smoking.

TABLE 2.4 Drugs Causing Induction or Inhibition of Cytochrome P450 Enzymes

Cytochrome P450 Isoenzyme	Inducers	Inhibitors
CYP1A2	Phenytoin	Ciprofloxacin
	Rifampin	Diltiazem
CYP2D6		Ranitidine
		Fluoxetine
CYP3A4	Carbamazepine	Diltiazem
	Corticosteroids	Fluoxetine
	Rifampin	Erythromycin

CYP, Cytochrome P450 oxidase system.

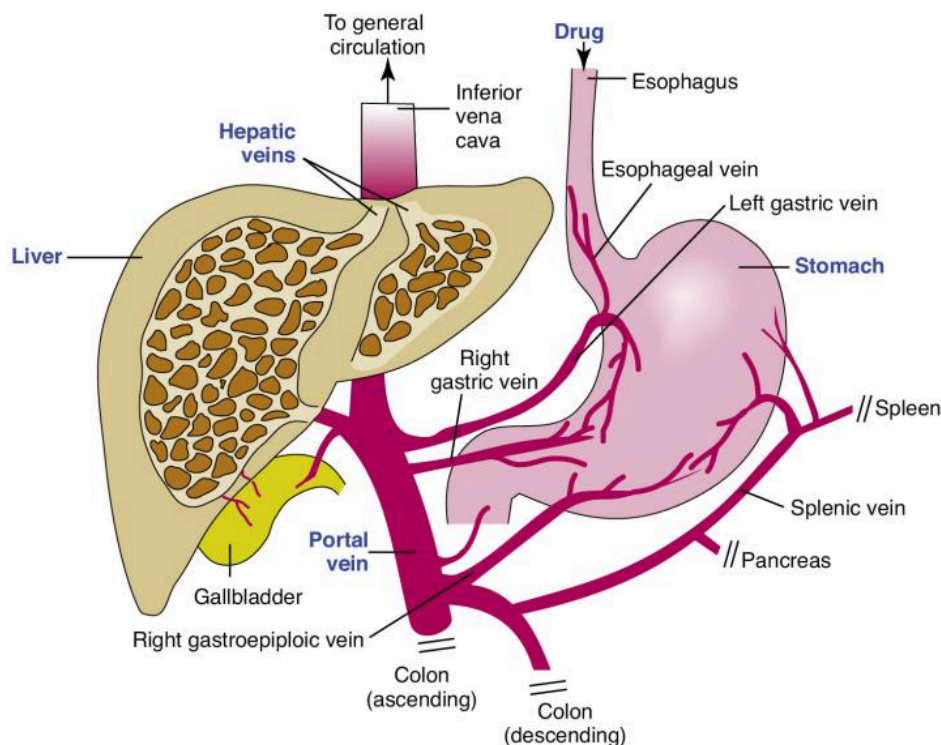
First-Pass Effect

Another clinically important effect of the liver on drug metabolism is referred to as the **first-pass effect** of elimination. When a drug is taken orally and absorbed into the blood from the stomach or intestine, the portal vein drains this blood directly into the liver (Fig. 2.3). Blood is drained from the liver by the right and left hepatic veins directly into the inferior vena cava and on into the general circulation.

If a drug is highly metabolized by the liver enzymes and is administered orally, most of the drug's activity is terminated in its passage through the liver before it ever reaches the general circulation and the rest of the body. This is the first-pass effect. Examples of drugs with a high first-pass effect are propranolol; nitroglycerin (sublingual administration is preferred to oral administration); and fluticasone propionate, an aerosolized corticosteroid. The first-pass effect causes difficulties with oral administration that must be overcome by increasing the oral dose (compared with the parenteral dose) or by using a delivery system that circumvents first-pass metabolism. The following routes avoid first-pass circulation through the liver: injection, buccal or sublingual (e.g., tablets), transdermal (e.g., patch), rectal (e.g., suppositories), and inhalation. These routes of administration bypass the portal venous circulation, allowing drugs to be generally distributed in the body before being circulated through the liver and ultimately metabolized. They also bypass metabolic degradation occurring in the gut as a result of specific metabolic enzymes (e.g., CYP3) or bacterial flora.

Elimination

The primary site of drug excretion in the body is the kidney, just as the liver is the site of the majority of drug metabolism. The kidney is important for removing the drug metabolites produced by the



• **Fig. 2.3** Anatomy of venous drainage from the stomach that forms the basis for the first-pass effect of orally administered drugs.

liver. Some drugs are not metabolized and are eliminated from the circulation entirely by the kidney. The route of elimination becomes important when choosing between alternative therapies because liver or kidney disease can alter the clearance of a drug by these organs. Generally, *clearance* is a measure of the ability of the body to rid itself of a drug. Most often, clearance is expressed as *total systemic* or *plasma clearance* to emphasize that all of the various mechanisms by which a given drug is cleared (e.g., metabolism, excretion) are taken into account.

Plasma Clearance

The term V_D is an abstraction that does not usually correspond to any real physiologic volume, and similarly, the term *plasma clearance* (Cl_p) refers to a hypothetical volume of plasma that is completely cleared of a drug over a given period. Consequently, Cl_p is usually expressed as liters per hour (L/hr) or, if body weight is taken into account, liters per hour per kilogram (L/hr/kg). Because Cl_p gives an indication of the quantity of drug removed from the body over a given period, it can be used to estimate the rate at which a drug must be replaced to maintain a steady plasma level.

Maintenance Dose

To achieve a steady level of drug in the body, dosing must equal the rate of elimination:

$$\text{Dosing rate (mg/hr)} = (Cl_p)(L/hr) \times \text{Plasma concentration (mg/L)}$$

Example

The clearance of theophylline is given as 2.88 L/hr/70 kg. For an average 70-kg adult, to maintain a plasma drug level of 15 mg/L (equivalent to 15 mcg/mL), calculate the dosing rate as follows:

$$\text{Dosing rate} = 2.88 \text{ L/hr} \times 15 \text{ mg/L} = 43.2 \text{ mg/hr}$$

The preceding simplified calculation assumes total bioavailability of the drug, which may not be true for some routes of administration, and is intended for conceptual illustration only. Actual patient treatment must take other factors into account. The drug could be given by constant infusion or divided into dosing intervals (e.g., where half the daily dose is given every 12 hours). When deciding on a dosing interval, it is desirable to know the *plasma half-life*.

Plasma Half-Life

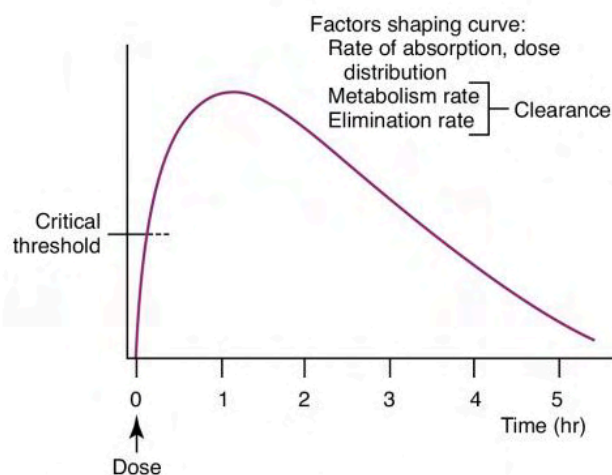
The *plasma half-life* ($T_{1/2}$) (the time required for the plasma concentration of a drug to decrease by one half) is a measure of how quickly a drug is eliminated from the body. More pertinent to dosing schedules, however, $T_{1/2}$ indicates how quickly a drug can accumulate and reach steady-state plasma levels. Drugs with a short $T_{1/2}$ (e.g., amoxicillin) reach steady-state levels quickly and must be given more frequently to maintain plasma levels, whereas the opposite is true of drugs with a long $T_{1/2}$, such as digoxin. Table 2.5 lists selected drugs in common use with their plasma half-lives.

Time-Plasma Curves

The concentration of a drug in the plasma over time can be graphed as a time-plasma curve (Fig. 2.4). The shape of this curve describes the interplay of the kinetic factors of absorption, distribution, metabolism, and elimination. These curves can indicate whether the dose given is sufficient to reach and maintain the critical

TABLE 2.5 Plasma Half-Lives of Common Drugs

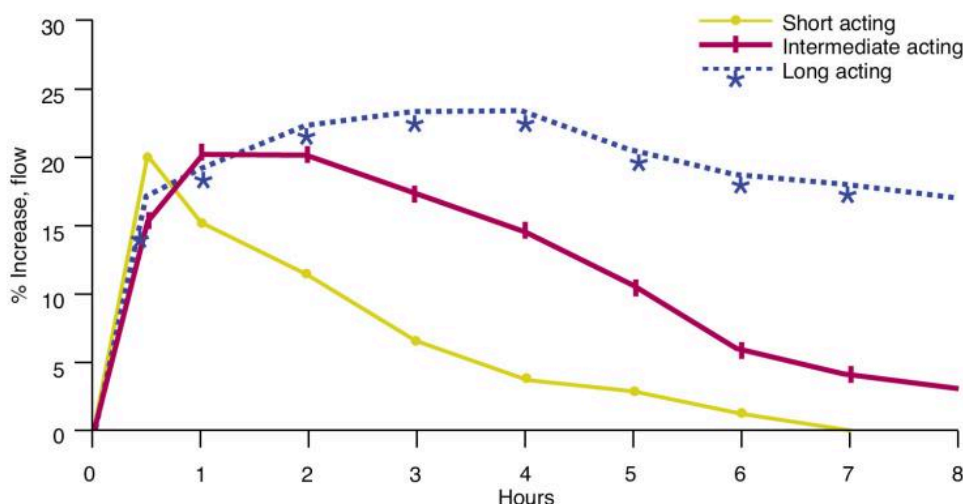
Drug	Half-Life (hr)
Acetaminophen	2.0
Amoxicillin	1.7
Azithromycin	40.0
Digoxin	39.0
Gabapentin	6.5
Morphine	1.9
Paroxetine	17.0
Terbutaline	14.0



• **Fig. 2.4** Plasma concentration of a drug over time. The critical threshold is the minimal level of drug concentration needed for a therapeutic effect.

threshold of concentration needed to achieve the desired therapeutic effect. Such a curve can also be plotted for concentrations of an aerosol drug in respiratory tract secretions. However, the duration of the *clinical effect*, rather than the concentration of the drug, is often represented in studies of aerosol drugs, particularly bronchodilators. The clinical effect is more helpful than a blood level in describing the pharmacokinetics of inhaled aerosols, which rely on topical delivery with a local effect in the airway.

Fig. 2.5 illustrates hypothetical curves for the peak effect and duration of effect of three bronchodilator drugs on expiratory flow rates. The short-acting curve could represent a drug, such as racemic epinephrine, an ultrashort-acting catecholamine bronchodilator. On the basis of its time curve, this agent is too short acting for maintenance therapy and is not β receptor specific. The intermediate curve could represent such an agent as albuterol, which has a peak effect of 30 to 60 minutes by inhalation and a duration of action of approximately 4 to 6 hours. These kinetics are useful for as-required bronchodilation or for maintenance therapy if a patient needs the drug four times daily. The kinetics indicate that bronchodilation with albuterol, an intermediate-acting drug, would not be maintained during an entire night. Finally, a long-acting agent, such as the bronchodilator salmeterol, could provide a 12-hour duration of effect, although time to peak effect is slower



• **Fig. 2.5** Hypothetical time-effect curves for three different bronchodilating agents, illustrating onset, peak effect, and duration.

(<2 hours). These kinetics are useful for convenient twice-daily dosage and around-the-clock bronchodilation. This example illustrates how pharmacokinetics of an inhaled aerosol can help determine the choice of a particular drug for a given clinical application and the dosage schedule needed to achieve the therapeutic effect. Other factors in the choice of a drug, whether inhaled aerosol, oral, or injectable, include the side effect profile, the individual's reaction to the drug, allergies, and compliance factors (patient adherence to dosage instructions), such as delivery formulations and dose timing.

Pharmacokinetics of Inhaled Aerosol Drugs

The inhalation route used for therapeutic aerosols, together with the physicochemical nature of the drug, determines the absorption, distribution, metabolism, and elimination of the aerosol drug.

Local Versus Systemic Effect

Inhaled aerosols are deposited on the surface of the upper or lower airway and are a form of topically administered drug. As topically deposited agents, inhaled aerosols can be intended either for a local effect in the upper or lower airway or for a systemic effect because the drug is absorbed and distributed in blood. A *local effect* is exemplified by a nasally inhaled vasoconstricting agent (decongestant), such as oxymetazoline (Afrin), or by an inhaled bronchodilator aerosol, such as albuterol (Proventil-HFA, Ventolin-HFA, Proair HFA). A systemic effect might be exemplified by the administration of inhaled zanamivir (Relenza) to treat influenza, inhaled morphine for pain control, or inhaled insulin aerosol for systemic control of diabetes.²

Inhaled Aerosols in Pulmonary Disease

Inhaled aerosols used in the treatment of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF), are intended for a local, targeted effect in the lung and airway. The rationale for the inhalation route in therapy of the lung is to maximize lung deposition while minimizing body (systemic) exposure and unwanted side effects. If the ratio of drug in the lung is high relative to the amount of drug in the overall body (systemic drug level), the inhalation route offers an

advantage over direct systemic administration (oral, intravenous) in treating the lung.

Distribution of Inhaled Aerosols

KEY POINT

The inhaled route of administration can involve both gastrointestinal and lung distributions. The systemic level of an inhaled drug and possible extrapulmonary side effects depend on both gastrointestinal and lung absorption of the active drug.

Because a portion of an inhaled aerosol is swallowed, the inhalation route leads to gastrointestinal absorption as well as lung absorption of the drug (Fig. 2.6). After inhalation of an aerosol by a spontaneously breathing patient without the use of artificial airway, a proportion of the aerosol exerts an impact in the oropharynx and is swallowed, and a proportion is inhaled into the airway. The traditional percentages given for stomach and airway proportions, based on Newman's classic measures³ in 1981 with an MDI, are approximately 90% (stomach) and 10% (airway). Similar percentages have been found with other aerosol delivery devices; however, newer devices are able to deliver more to the airway, assuming use of good technique.

Approximately 50% to 60% of the drug impacts in the mouth or oropharynx and contributes to the 90% reaching the stomach. These amounts are used in discussing the pathways of metabolism for an inhaled drug. Although the remaining 10% is traditionally accepted as the proportion of inhaled drug that reaches the lower respiratory tract when delivered via currently available devices, the exact percentage can vary from 10% to 30% with different delivery devices or techniques of patient use. Lung deposition with an inhaled corticosteroid, budesonide (Pulmicort), has been reported as 15% with a pressurized MDI (pMDI) and 32% with a DPI⁴ (Pulmicort Turbuhaler; AstraZeneca, Wilmington, Delaware). Use of reservoir devices with MDIs or delivery through endotracheal tubes can significantly change oropharyngeal impaction or airway delivery (see Chapter 3).

Oral Portion (Stomach). The swallowed aerosol drug is subject to gastrointestinal absorption, distribution, and metabolism, just like an orally administered drug. The aerosol drug can be absorbed

The **lung availability/total systemic availability ratio (L/T ratio)** quantifies the efficiency of aerosol drug delivery to the lung and is based on the distribution to the airway and gastrointestinal tract just described. For an aerosol drug (e.g., a bronchodilator or corticosteroid) that targets the respiratory tract, the L/T ratio can be defined as the proportion of drug available from the lung, out of the total systemically available drug.

The *clinical* or *therapeutic effect* of a bronchoactive aerosol comes from the inhaled drug deposited in the airways. The *systemic* or *extrapulmonary side effects* come from the total amount of drug absorbed into the system. The total systemic drug level is caused by airway absorption plus the amount absorbed from the gastrointestinal tract. The L/T ratio can quantify and compare the efficiency of drug delivery systems targeting the respiratory tract. Any action that reduces the swallowed portion of the inhaled drug, such as a reservoir device (spacer, holding chamber), or high first-pass metabolism, can increase the L/T ratio. Factors that can increase the L/T ratio are summarized in [Box 2.3](#). A perfectly efficient inhalation device would deliver all of the drug to the lung and none to the oropharynx or gastrointestinal tract, giving a ratio of 1 (lung availability = total systemic availability; all systemic drug comes only from the lung absorption).

CLINICAL CONNECTION

A respiratory therapist (RT) can increase the L/T ratio by properly instructing the patient in the use of the aerosol device. Additionally, the use of a breath hold may increase L/T ratio by assisting in deposition of aerosol particles.

This concept was proposed in 1991 by Borgström⁵ and elaborated on by Thorsson.⁶ An example, based on the data of Thorsson for albuterol inhalation using two different delivery devices, is given in [Fig. 2.7](#). With use of an MDI, approximately 30% of the

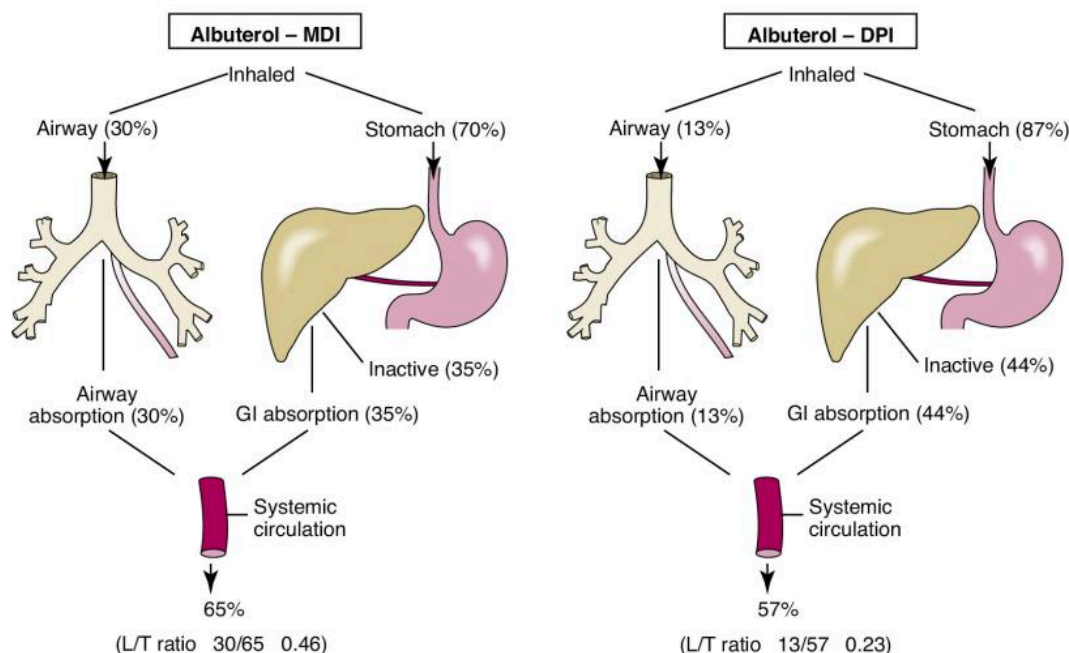
inhaled drug reaches the lung, with 70% going to the stomach. With complete absorption from the stomach, half of this 70% is broken down in the liver so that 35% reaches the systemic circulation. The total amount of the original 100% dose reaching the circulation is 65% (lung, 30%; stomach and liver, 35%). Because 30% of the 65% comes from the lung, this gives an L/T ratio of $30/65 = 0.46$.

The data for the DPI, using a Rotahaler (GlaxoSmithKline, Research Triangle Park, North Carolina), which is no longer available, give an L/T ratio of 0.23 (lung, 13%; stomach and liver, 44%). On the basis of these ratios, inhalation of albuterol via an MDI gives more efficient lung delivery with less systemic availability compared with inhalation via a DPI, such as the Rotahaler. With the MDI, 46% of the systemic exposure is from the lung, whereas with the DPI, 23% is from the lung. A high L/T ratio is desired; [Table 2.6](#) gives examples of various L/T ratios, along with lung deposition for several drugs and delivery devices.

The L/T ratio is determined by the rate of first-pass metabolism and the efficiency of the inhalation device in placing the drug in the airway. A high L/T ratio can be achieved even with poor lung delivery and efficient stomach absorption if there is a high first-pass effect on the swallowed drug. Comparisons of L/T ratios must be

• BOX 2.3 Factors Increasing Lung Availability/Total Systemic Availability Ratio With Inhaled Drugs

- Efficient delivery devices (high airway and low gastrointestinal delivery)
- Inhaled drugs with high first-pass metabolism
- Mouthwashing, including rinsing and spitting
- Use of a reservoir device (spacer, holding chamber) to decrease oropharyngeal deposition and swallowed drug amount



• **Fig. 2.7** The lung availability/total systemic availability (L/T) ratio can quantify the efficiency of aerosol drug delivery to the respiratory tract by partitioning relative amounts from the gastrointestinal tract and from the respiratory tract (see text for explanation). *DPI*, Dry powder inhaler; *GI*, gastrointestinal; *MDI*, metered dose inhaler. (Data from Thorsson. L. [1995]. Influence of inhaler systems on systemic availability, with focus on inhaled corticosteroids. *Journal of Aerosol Medicine*, 8[Suppl 3], S29.)

TABLE
2.6**Lung Availability/Total Systemic Availability Ratios for Several Inhaled Drugs With Various Aerosol Delivery Devices***

Drug	Device	Lung Deposition (%)	L/T Ratio	Subjects
Albuterol	pMDI	18.6	0.36	Patients—good coordinators
		7.2	0.17	Patients—poor coordinators
	BAI (pMDI)	20.8	0.41	Patients—poor coordinators
	Turbuhaler	23.2	0.45	Healthy volunteers
Budesonide	pMDI (CFC)	15	0.66	Healthy subjects
	Turbuhaler	32	0.87	Healthy subjects
	MDI (HFA) [†]	59	0.92	Patients

*All drug amounts are expressed as percentages of metered or nominal dose.

[†]Data from Harrison, L.I. (2002). Local versus total systemic bioavailability of beclomethasone dipropionate CFC and HFA metered dose inhaler formulations. *Journal of Aerosol Medicine*, 15, 401 [erratum (2003) in *Journal of Aerosol Medicine*, 16, 97].

BAI, Breath-actuated inhaler; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; L/T ratio, lung availability/total systemic availability; pMDI, pressurized metered dose inhaler.

Data from Borgström, L. (1998). Local versus total systemic bioavailability as a means to compare different inhaled formulations of the same substance. *Journal of Aerosol Medicine*, 11, 55.

between the *same* drugs with different delivery devices. Two drugs with different first-pass metabolism rates can have different L/T ratios even if the airway deposition or delivery device is the same. A good example is provided in Table 2.6, in the comparison of albuterol and budesonide, both administered via a Turbuhaler DPI. Albuterol and budesonide have first-pass metabolism rates of 50% and 90%, respectively. With approximately the same lung delivery of 22% to 23% for both drug–device systems, the L/T ratio is 0.45 for albuterol but 0.87 for budesonide. The improved L/T ratio of budesonide compared with albuterol is not caused by a difference in device efficiency but by the higher rate of metabolism of budesonide that reduces systemic blood levels from gastrointestinal absorption. The L/T ratio also suggests that aerosol delivery devices should be evaluated together with the drug to be used. “Each combination of active drug and device is a unique pharmaceutical formulation, as both the drug itself and the device can influence the overall properties of the formulation.”⁵ The L/T ratio does not determine whether systemic toxicity or side effects will occur. First, systemic effects depend on the amount of active drug absorbed into the system, whether from the lung or from the gastrointestinal tract. An inhaled corticosteroid, such as fluticasone, is rapidly metabolized in a first-pass effect. As a result, the swallowed portion gives minimal systemic levels. Good absorption of the aerosol drug from the lungs in sufficiently high doses could, however, cause systemic effects. Second, delivery to the oropharynx and gastrointestinal tract by a less efficient aerosol delivery device or method may be irrelevant if the drug is largely inactivated when taken orally and causes no local oropharyngeal effects. Catecholamine bronchodilators would be examples of such a drug. The L/T ratio indicates clearly how close an aerosol drug delivery system comes to the ideal of having all of the systemic drug exposure come from only the lung dose.

Pharmacodynamic Phase

KEY POINT

Pharmacodynamics describes the mechanism of activity by which drugs cause their effects in the body. The principal concept is the drug target protein (e.g., drug receptor).

The mechanism of drug action by which a drug molecule causes its effect in the body is the pharmacodynamic phase. Most drugs exert their effects by binding to protein targets and subsequently modulating the normal function of these proteins, usually inducing physiologic changes that affect multiple tissues and organ systems. The relevant protein targets include receptors, enzymes, ion channels, and carrier molecules. A receptor is any cell component that combines with a drug to change or enhance the function of the cell. In addition, some drugs exert their main therapeutic effect by interacting with DNA rather than by binding directly to proteins. The chemotherapeutic agent cisplatin inhibits cell division by binding to and disrupting cancer cell DNA, and the antiviral drug ganciclovir inhibits herpes virus replication by insinuating itself in the viral DNA and stopping further transcription.

Structure–Activity Relationships

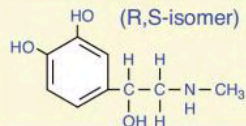
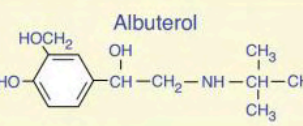
The matching of a drug molecule with a receptor or enzyme in the body is based on a structural similarity between the drug and its binding site. The relationship between the chemical structure of a drug and its clinical effect or activity is termed the **structure–activity relationship (SAR)**. Isoproterenol and albuterol are examples of two aerosol bronchodilators whose differing structures cause different pharmacokinetic activity and tissue responses.

The structures of isoproterenol and albuterol are illustrated in Fig. 2.8, with a summary of two critical differences in their pharmacokinetic profile and one critical difference in their side effects (heart rate increase). Although the two structures are very similar, and both are in the same family of β -adrenergic bronchodilators (see Chapter 6 for a discussion of this class of drugs), they are different. Isoproterenol is a catecholamine, which is metabolized rapidly because it is absorbed in the airway by the enzyme catechol *O*-methyltransferase (COMT), giving it a short duration of action. Albuterol, a saligenin, is not a substrate for the enzyme COMT but is, instead, metabolized through sulfate conjugation, a slower process. This difference is caused by the substitution of HOCH_2 for the OH group at the carbon-3 position. In addition, the structures of the two side chains are sufficiently different to change their receptor selectivity. Isoproterenol matches to receptors found in the airway (β_2 receptors) and the heart (β_1 receptors), whereas albuterol is more selective for receptors in the airway only. In recommended doses, albuterol has little or no effect on heart rate; however, isoproterenol usually causes an increase in heart rate.

Nature and Type of Drug Receptors

KEY POINT

Two mechanisms of drug–receptor action form the basis for the effects of two drug classes in respiratory care: intracellular receptor binding and modified gene transcription by lipid-soluble drugs (glucocorticoids) and receptors linked to their effector systems by G proteins (β -adrenergic bronchodilators).

 (R,S-isomer)	 Albuterol	
Structure:	Catecholamine	Saligenin (Catecholamine analogue)
Pharmacokinetics:	Peak effect: 20 min Duration: 1.5–2 hr	Peak effect: 30–60 min Duration: 4–6 hr
Side effect:	Increased heart rate	Little/no change in heart rate
Class of drug:	Adrenergic bronchodilator	Adrenergic bronchodilator
Therapeutic effect:	Relax airway, smooth muscle	Relax airway, smooth muscle

• **Fig. 2.8** Structure–activity relationships for two drugs representing the same class of bronchodilator. Racemic epinephrine and albuterol are both β -adrenergic agents, with minor structural differences leading to significantly different clinical effects.

At present, drugs having the greatest relevance to respiratory therapy act through receptor proteins, although enzymes are important targets for some antibiotics, antiviral drugs, and antihypertensive drugs. Receptors for many drugs have been biochemically purified and directly characterized, whereas in the past, such receptors were only indirectly inferred from drug action and differences of action between similar drugs.

Drug Receptors

Most drug receptors are proteins, or polypeptides, whose shape and electric charge provide a match to a drug's corresponding chemical shape or charge. Drug–receptor proteins include receptors on cell surfaces and within the cell.

The process by which attachment of a drug to its receptor results in a clinical response involves complex molecular mechanisms. This process sends a signal from the drug chemical into an intracellular sequence that controls cell function. Usually, the drug attaches to a receptor protein that spans the cell membrane, so the process is one of “transmembrane signaling.”

Four mechanisms for transmembrane signaling are well understood. Each mechanism can transduce signals for a group of different drug receptors and for different drugs. The four mechanisms are as follows:

1. Lipid-soluble drugs cross the cell membrane and act on intracellular receptors to initiate the drug response. *Examples:* corticosteroids, vitamin D, thyroid hormone.
2. The drug attaches to the extracellular portion of a protein receptor, which projects into the cell cytoplasm (a “transmembrane protein”) and activates an enzyme system, such as tyrosine kinase, in the intracellular portion to initiate an effect. *Examples:* insulin, platelet-derived growth factor (PDGF).
3. The drug attaches to a surface receptor that regulates the opening of an ion channel. *Examples:* acetylcholine receptors on skeletal muscle, γ -aminobutyric acid (GABA).
4. The drug attaches to a transmembrane receptor that is coupled to an intracellular enzyme by a G protein (guanine nucleotide–regulating protein). *Examples:* β -adrenergic agents, acetylcholine at parasympathetic nerve endings.

The first, third, and fourth mechanisms are reviewed in more detail in the following sections because these are the basis for the activity of drugs commonly used in respiratory care.

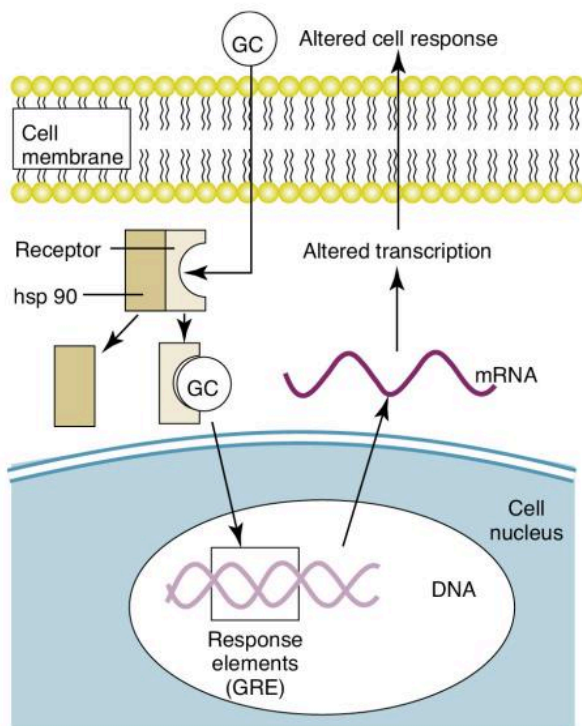
Lipid-Soluble Drugs and Intracellular Receptor Activation

Intracellular receptor activation by lipid-soluble drugs is the basis on which corticosteroids, an important class of drugs in respiratory care, cause a cell response. Examples of corticosteroid drugs are inhaled beclomethasone and flunisolide and oral prednisone. In this drug–receptor mechanism, the drug is sufficiently lipid soluble to cross the lipid bilayer of the cell membrane, diffuse into the cytoplasm, and attach to an intracellular polypeptide receptor. The drug–receptor complex translocates to the cell nucleus and binds to specific DNA sequences termed *hormone response elements*, which can either stimulate or repress the transcription of genes in the nucleus. An example of such drug–receptor signaling is given in Fig. 2.9, for glucocorticoid drugs, such as inhaled flunisolide or oral prednisone. The glucocorticoid diffuses across the cell membrane and attaches to a receptor in the cytoplasm. Attachment of the drug to the receptor causes displacement of certain proteins, termed *heat shock proteins*, and a change in the receptor configuration to an active state. The newly coupled drug–receptor complex moves or *translocates* to the nucleus of the cell, where it pairs with other drug–receptor complexes, which then bind to a glucocorticoid response element (GRE) of the cell's DNA. This binding initiates or represses cell response and transcription of target genes (see Chapter 11 for a discussion of the mechanism and effects of glucocorticoids).

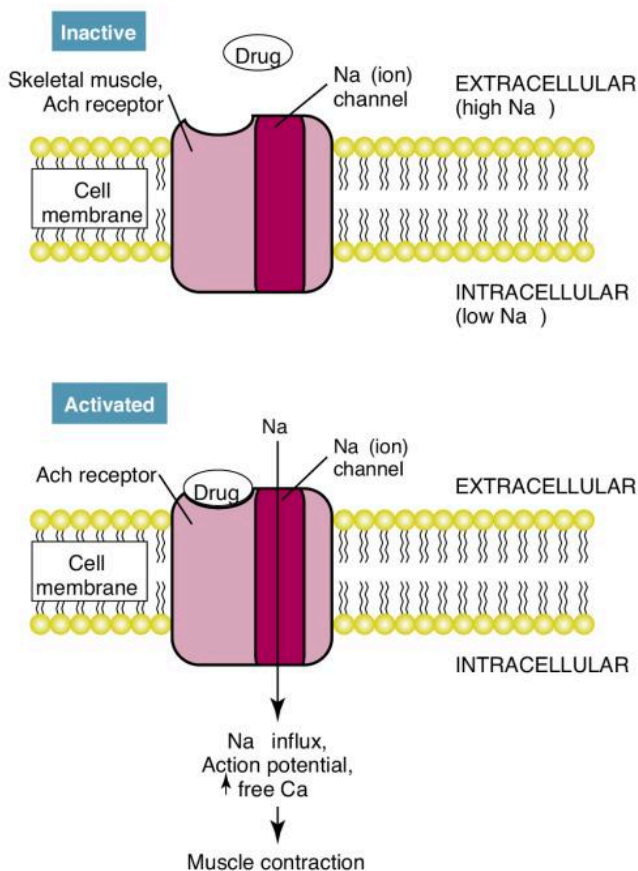
Drugs that act by diffusing into the cell and regulating gene responses have longer periods for observed responses, ranging from 30 minutes to several hours. Typically, there is also a persistence of effect for hours or days, even after the drug has been eliminated from the body.

Drug-Regulated Ion Channels

Another process of drug signal transduction regulates the flow of ions, such as sodium or potassium, through cell membrane channels. This has been depicted in Fig. 2.10. The drug binds to a receptor on the cell membrane surface. The receptor has a portion above or on the surface of the cell membrane and extends through the membrane into the cytoplasm of the cell. When activated by the drug (or by an endogenous ligand), the receptor opens an ion channel to allow increased transmembrane conductance of an ion. An example of such a receptor is that for acetylcholine, a neurotransmitter, on skeletal muscle. This acetylcholine receptor



• **Fig. 2.9** Diagram of the mechanism of action for lipid-soluble drugs, such as glucocorticoids, which bind to intracellular receptors and then modify cell nuclear transcription. GC, Glucocorticoid; GRE, glucocorticoid response element; hsp 90, heat shock protein 90.



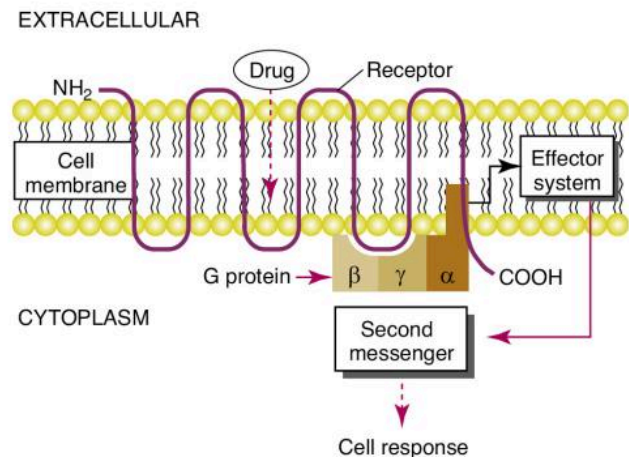
• **Fig. 2.10** Illustration of the drug signal mechanism that regulates ion channel flow to cause a drug response, such as that of acetylcholine (ACh) or nicotine in stimulating skeletal muscle fibers to contract.

is termed a *nicotinic receptor* because it responds to the substance nicotine as well as acetylcholine. Attachment of acetylcholine or nicotine opens an ion channel and allows the high sodium (Na^+) concentration in extracellular fluid to flow into the lower concentration of the cell. This produces a reversal of voltage, or *depolarization*, and a corresponding muscle twitch. Acetylcholine is the neurotransmitter for voluntary muscle contraction and movement, and stimulation by nicotine can increase skeletal muscle tremor.

Receptors Linked to G Proteins

G protein-linked receptors mediate bronchodilation and bronchoconstriction in the airways in response to endogenous stimulation by the neurotransmitters epinephrine and acetylcholine. These same airway responses can be elicited by adrenergic bronchodilator drugs (discussed in Chapter 6) or blocked by acetylcholine-blocking (anticholinergic) agents, such as ipratropium bromide (discussed in Chapter 7). G proteins and G protein-linked receptors also mediate the effects of other chemicals, including the effects of histamine and glucagon, and the phototransduction of light in retinal rods and cones. Drug-receptor signaling with G protein-linked receptors involves three main components: the *drug receptor*, *G protein*, and *effector system*. When a drug attaches to a G protein-linked receptor, these three components interact to cause a cellular response to the drug. The effector system triggers the cell response by activating or inhibiting a *second messenger* within the cell. Fig. 2.11 shows the main elements of a G protein-linked receptor. Each of the major elements in this signaling mechanism complex is described briefly, along with the dynamics of their interaction.

Receptors that couple with G proteins have been well characterized and show a similar structure in which a polypeptide chain crosses the cell membrane seven times, giving a serpentine appearance to the receptor. The polypeptide chain has an amino



Example:	
Drug:	β -adrenergic bronchodilator
Receptor:	β -receptor
G Protein:	Gs
Effector:	adenylyl cyclase
Second messenger:	cyclic 3',5',-AMP

• **Fig. 2.11** Simplified diagram of the components by which a G protein-linked receptor causes a cell response: drug, receptor, G protein, effector system, and second messenger. Each of these components is identified in this example of a β -adrenergic bronchodilator drug and the β receptor, which is a G protein-linked receptor. Gs, Stimulatory G protein.

(NH₂, or N) terminal site outside the cell membrane and a carboxyl (COOH, or C) terminal inside the cell. Although the seven transmembrane segments of the receptor are depicted in Fig. 2.12 as being positioned side by side, the receptor appears to form a cylindrical structure if viewed perpendicular to the surface of the cell membrane, with the transmembrane loops forming the sides of the cylinder. The drug usually couples to the receptor at a site surrounded by the transmembrane regions of the receptor protein, that is, within the interior of the cylinder. The receptor activates a G protein on the cytoplasmic (inner) surface of the cell membrane. The site of the interaction of the G protein with the receptor polypeptide is thought to be at the third cytoplasmic loop of the receptor chain.

G proteins are so termed because they are a family of guanine nucleotide-binding proteins with a three-part, or *heterotrimeric*, structure. The three subunits of the G protein are designated by the Greek letters alpha (α), beta (β), and gamma (γ). The α subunit differentiates members of the G protein family. On the basis of the α subunit, the G protein is classified into subgroups, such as G_s, which *stimulates* an effector system, and G_i, which *inhibits* the

effector system. Other types of G proteins have been identified as well; however, they are not reviewed in this chapter.

The activated G protein changes the activity of an *effector system*, which may be either an enzyme, which catalyzes the formation of a *second messenger*, or an ion channel, which allows the outflow of potassium (K⁺) ions from the cell. One of the second messengers is the well-known cyclic adenosine 3', 5'-monophosphate (cAMP). The effector enzyme for increasing cAMP is adenylyl cyclase (previously termed adenylyl cyclase), which converts adenosine triphosphate (ATP) to cAMP. The G protein that stimulates adenylyl cyclase is the G_s (for *stimulatory*) protein. β receptors, which couple with β -adrenergic bronchodilators, activate G_s proteins. Another G protein, G_i (for *inhibitory*), inhibits the activation of adenylyl cyclase; G_i proteins are activated by cholinergic (muscarinic) agonists, such as acetylcholine or the drug methacholine.

The dynamics of cell signaling by G protein-linked receptors are illustrated schematically in Fig. 2.12. When there is no drug attached to the receptor site, the α subunit of the G protein is bound to guanosine diphosphate (GDP), and the G protein is in an inactive state. When a drug attaches to the receptor, there is a change in the receptor conformation that causes the release of GDP and the binding of guanosine triphosphate (GTP) to the α subunit. This is the active state for the G protein. The GTP-bound α subunit dissociates, or *unlinks*, from the β - γ portion and couples with the effector system to stimulate or inhibit a second messenger within the cell. The GTP bound to the α subunit is hydrolyzed by a guanosine triphosphatase (GTPase) enzyme, dissociates from the effector, and reassociates with the β - γ dimer. The G protein-linked receptor is then ready for reactivation.

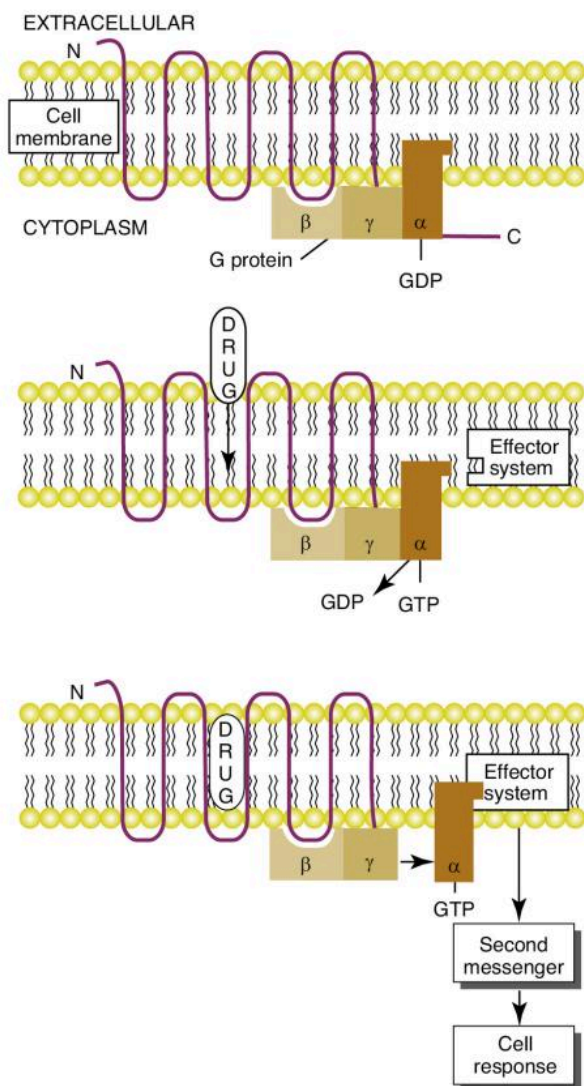
Details on specific G proteins, their effector systems, and their second messengers are presented for neurotransmitters, such as epinephrine and acetylcholine in the nervous system (see Chapter 5), and for the classes of drugs that link to such receptors, such as adrenergic bronchodilators (see Chapter 6) and anticholinergic bronchodilators (see Chapter 7).

Dose-Response Relationships

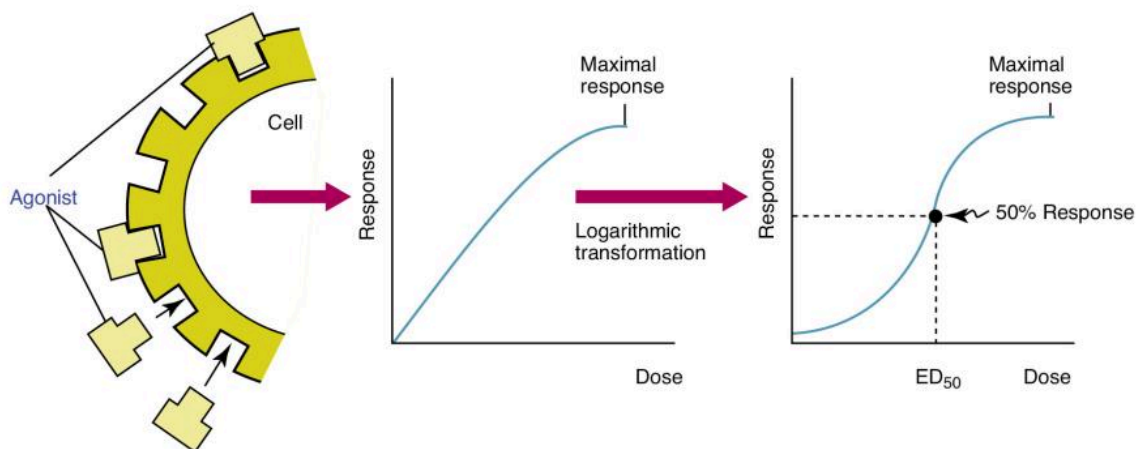
KEY POINT

Various terms describe the dose-response relationship of drugs, while they combine with their corresponding receptors, and drug interactions: *potency*, *maximal effect*, *therapeutic index (TI)*, *agonists* and *antagonists*, *synergism*, *additivity*, *potentiation*, and reaction types, such as *idiosyncrasy*, *hypersensitivity*, *tolerance*, and *tachyphylaxis*.

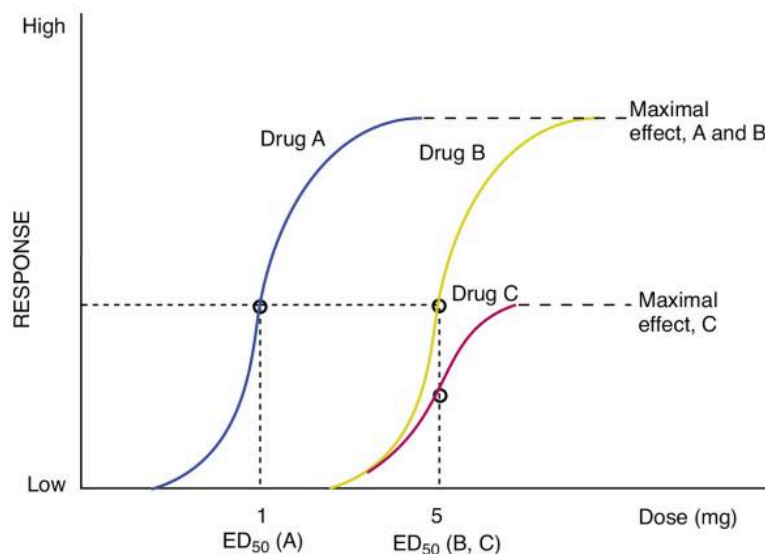
The response to a drug is proportional to the drug's concentration. As drug concentration increases, the number of receptors occupied increases, and the drug effect also increases up to a maximal point; this is graphed as a dose-response, or concentration-effect, curve (Fig. 2.13). Increasing amounts of a drug increase the response in a fairly direct fashion; however, the rate of response usually diminishes as the dose increases until a plateau of maximal effect is reached. Such a convex, or *hyperbolic*, curve is normally transformed mathematically by using the logarithm of the dose so that a sigmoid curve is obtained. The linear midportion of a sigmoid curve allows for easier comparison of the dose-response curve for different drugs. In particular, the dose at which 50% of the response to the drug occurs is indicated in Fig. 2.13 and is referred to as the ED_{50} , the dose of drug that produces 50% of the maximal effect. This value may also be denoted as the EC_{50} , for effective concentration giving 50% of maximal response.



• **Fig. 2.12** Sequential diagram of G protein-linked receptor activation and G protein function in linking a drug signal to a cell response.



• **Fig. 2.13** Illustration of the dose–response curve (left), showing an increasing effect that ultimately plateaus, and its logarithmic transformation to produce a sigmoid curve (right). ED_{50} , Drug dose that produces 50% of the maximal effect.



• **Fig. 2.14** The potency of a drug is defined as the dose producing 50% of the drug's maximal effect. Drug A is more potent than drug B; however, drugs B and C are equally potent, although drug C has less maximal effect than drug B.

Potency Versus Maximal Effect

Dose–response curves are the basis for defining and illustrating several concepts used to characterize and compare drugs. Two concepts that allow comparison of drugs are potency and maximal effect, both illustrated in Fig. 2.14.

1. **Potency:** Refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug producing 50% of the *maximal response* of the drug. The potency of two drugs, A and B, can be compared on the basis of the ED_{50} values of the two drugs: relative potency, $A \text{ and } B = ED_{50}(B)/ED_{50}(A)$.

2. **Maximal effect:** The greatest response that can be produced by a drug, a dose above which no further response can be elicited.

The lower the ED_{50} for a given drug, the more potent is the drug, as shown in Fig. 2.14. Curves for drugs A and B show different potencies. If the ED_{50} for drug B is 5 mg and for drug A is 1 mg, then drug A is five times more potent than drug B:

$$ED_{50}(B)/ED_{50}(A) = 5 \text{ mg}/1 \text{ mg} = 5$$

Drug B requires five times the amount of drug A to produce 50% of its maximal effect. Potency is not the same as maximal effect, also illustrated in Fig. 2.14. *Potency* is relatively defined by using the ED_{50} values of two drugs, whereas *maximal effect* is absolutely defined as a physiologic or clinical response. The curves indicate that drugs B and C have the same potency; that is, the same dose produces 50% of the maximal response. However, drug B has a greater maximal effect compared with drug C. Because the ED_{50} is the dose causing a response that is half the maximal response of the *same* drug, two drugs can have different maximal responses but the same ED_{50} (and the same potency), as shown in Fig. 2.14.

Therapeutic Index

The **therapeutic index (TI)** can be defined as the ratio of the lethal dose for 50% of the test population (LD_{50}) to the ED_{50} for a given drug, with ED_{50} and LD_{50} indicating half of the test subjects, rather than a 50% clinical response. The TI is also based on the dose–response curve of a drug. However, instead of a graded clinical or

physiologic response, such as an increase in heart rate, we substitute an all-or-nothing response of improvement for each subject, or toxicity or death for each subject. In this case the ED_{50} represents the dose of the drug at which half of the test subjects improve. Similarly, the LD_{50} is the lethal dose for 50% of the test population. Doses are established for a test population of animals (as illustrated in Fig. 2.15).

The ratio of the dose that is toxic to 50% of test subjects to the dose that provides relief to 50% of the subjects is the clinical TI. This index represents the safety margin of the drug. The smaller the TI, the greater is the possibility of crossing from a therapeutic effect to a toxic effect. Theophylline is a drug used in respiratory care that has a narrow therapeutic margin. As a result, toxic side effects can be seen at close to therapeutic dose levels in some individuals.

Agonists and Antagonists

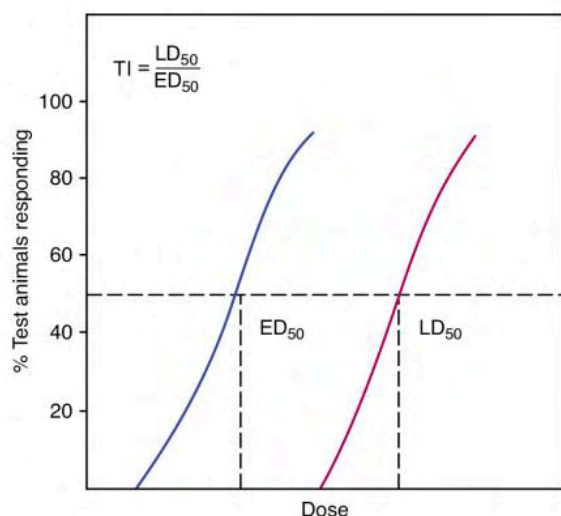
An **agonist** is a drug or chemical that binds to a corresponding receptor (has affinity) and *initiates* a cellular effect or response (has

efficacy). An **antagonist** is a drug or chemical that is able to bind to a receptor (has affinity) but causes no response (zero efficacy). Because the antagonist drug is occupying the receptor site, it can prevent other drugs or an endogenous chemical from reaching and activating the receptor site. By doing so, an antagonist *inhibits* or *blocks* the agonist at the receptor. Agonists are divided further into *full* and *partial* agonists. A full agonist is a drug that gives a higher maximal response than a partial agonist. The dose–response curves for a partial agonist and a full agonist are represented in Fig. 2.16. Both have receptor affinity, but a partial agonist has less efficacy than a full agonist.

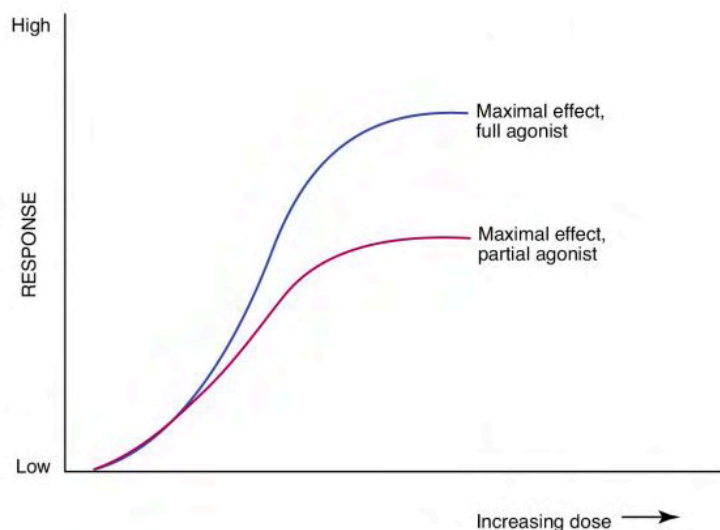
Drug Interactions

The concept of drug antagonism just discussed is an example of a drug interaction in which one drug can block the effect of another. Mechanisms of drug antagonism are as follows:

- **Chemical antagonism:** Direct chemical interaction between a drug and the biologic mediator that inactivates the drug. An example is chelation of toxic metals by a chelating agent.
- **Functional antagonism:** Can occur when two drugs each produce an effect and the two effects cancel each other. For example, methacholine can stimulate parasympathetic (muscarinic) receptors in the airways, causing bronchoconstriction; epinephrine can stimulate β_2 receptors in the airways, causing bronchodilation.
- **Competitive antagonism:** Occurs when a drug has affinity for a receptor but no efficacy and at the same time blocks the active agonist from binding to and stimulating the receptor. For example, fexofenadine is a competitive antagonist to histamine on specific receptors (H_1) on bronchial smooth muscle and the nasopharynx and is used to treat allergies to pollens.
- The following terms are used to describe positive interactions between two drugs:
- **Synergism:** Occurs when two drugs act on a target organ by different mechanisms of action, and the effect of the drug pair is greater than the sum of the separate effects of the drugs.
- **Additivity:** Occurs when two drugs act on the same receptors, and the combined effect is the simple linear sum of the effects of the two drugs, up to a maximal effect.
- **Potentiation:** A special case of synergism in which one drug has no effect but can increase the activity of the other drug.



• **Fig. 2.15** Therapeutic index (TI), defined as the ratio of the dose that is lethal for 50% of test animals (LD_{50}) to the dose causing improvement in 50% of test animals (ED_{50}).



• **Fig. 2.16** Dose–response curves for full and partial agonists, illustrating the greater maximal effect of the full agonist.

Terms for Drug Responsiveness

Individuals exhibit variation in their responses to drugs; the dose-response curves previously illustrated represent an average of an entire group. The following terms are encountered in pharmacology to describe individual reactions to drugs:

- **Idiosyncratic effect:** Effect that is the opposite of, or unusual, or an absence of effect, compared with the predicted usual effect in an individual.
- **Hypersensitivity:** Allergic or immune-mediated reaction to a drug, which can be serious, requiring airway maintenance or ventilatory assistance.
- **Tolerance:** Decreasing intensity of response to a drug over time.
- **Tachyphylaxis:** Rapid decrease in responsiveness to a drug.

Pharmacogenetics

KEY POINT

Pharmacogenetics refers to hereditary differences in the way the body handles specific drugs.

The well-described variations among patients in responses to drugs are being increasingly traced to hereditary differences. The study of these hereditary or genetic differences is referred to as **pharmacogenetics**. These genetic variations may not be manifested as an “abnormality” until the patient is challenged with a drug, at which time the irregularity in the pharmacokinetic or pharmacodynamic response is revealed. Genetic differences affecting drug metabolism have been most extensively studied, although variation in target proteins may be equally important.

Several examples can be given from drugs commonly seen in respiratory and critical care:

- **Isoniazid:** Antituberculosis drug whose rates of metabolism and inactivation vary among individuals, with evidence of rapid and slow inactivators. The proportion of rapid versus slow inactivators is about 50/50 among White and Black individuals, but Inuit and some Asian people tend to be rapid inactivators.
- **Succinylcholine:** Neuromuscular paralyzing agent used during surgery. Succinylcholine is normally metabolized by a butyrylcholinesterase enzyme (pseudocholinesterase). Approximately 1 in 3000 individuals has a genetically determined variant of this enzyme. As a result, a patient may take several hours to recover from the drug, rather than the several minutes usually seen, and may also begin to breathe spontaneously. Mechanical ventilatory support would be required until spontaneous breathing is adequate.
- **Isoflurane:** Inhalation anesthetic that (similar to several other related anesthetics) can cause malignant hyperthermia in genetically susceptible individuals. Patients with an atypical variant of a calcium release channel can die as a result of this serious complication of general anesthesia, which involves a rapid increase in body temperature and increased oxygen consumption.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. If a drug is in liquid solution, what routes of administration are available for its delivery, considering only its dosage form?
2. Although generic drug equivalents all have the same amount of active drug, do formulations of the same drug from different manufacturers all have the same ingredients?

3. If 200 mg of a drug results in a plasma concentration of 10 mg/L, what is the calculated volume of distribution (V_D)?
4. If the V_D of a drug, such as phenobarbital, is 38 L/70 kg, and an effective concentration is 10 mg/L, what loading dose would be needed for an average adult (assuming total bioavailability)?
5. If an inhaled aerosol has zero gastrointestinal absorption of an active drug and only lung absorption, what is the L/T ratio?
6. True or False: A patient uses a reservoir device with an inhaled aerosol, and there is no swallowed portion of the drug; therefore there are no systemic side effects.
7. Which receptor system signal mechanism is responsible for the effects caused by β -receptor activation, such as those seen with adrenergic bronchodilators (e.g., albuterol)?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A resident orders racemic epinephrine, a bronchodilator, to be given qid to a 67-year-old man. The patient has had chronic obstructive pulmonary disease (COPD) for the past 10 years and was admitted to the hospital the previous evening with a respiratory infection. At 8:00 AM, you administer the prescribed usual recommended dose of aerosol treatment via a nebulizer. After the treatment, the patient's respiratory rate is reduced from 26 breaths/min to 18 breaths/min, and there is less use of accessory muscles. Wheezing on auscultation is also decreased, although you hear adequate breath sounds bilaterally. He seems less short of breath. At 10:00 AM, he is exhibiting moderate respiratory distress, using accessory muscles, complaining of dyspnea, and having increased wheezing on auscultation. His next aerosol treatment is due at noon. He admits to no chest pain; wheezes and breath sounds can be auscultated over the entire thorax. You review the pharmacokinetics of racemic epinephrine and find the following:

1. **Onset:** 3 to 5 minutes
2. **Peak effect:** Approximately 15 minutes
3. **Duration:** Approximately 2 hours or less

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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3

Administration of Aerosolized Agents

DOUGLAS S. GARDENHIRE, RACHEL CULBRETH

CHAPTER OUTLINE

Physical Principles of Inhaled Aerosol Drugs

- Aerosol Particle Size Distributions
- Measurement of Particle Size Distributions
- Particle Size and Lung Deposition
 - Fine Particle Fraction
 - Particle Size and Therapeutic Effect
 - Mechanisms of Deposition
 - Effect of Temperature and Humidity

Aerosol Generators for Drug Delivery

- Nebulizers
 - Types of Small Volume Nebulizers
- Pressurized Metered Dose Inhalers
 - Technical Description
 - Chlorofluorocarbon Versus Hydrofluoroalkane Propellants
 - Types of Pressurized Metered Dose Inhalers
 - Factors Affecting Metered Dose Inhaler Performance
 - Correct Use of a Pressurized Metered Dose Inhaler
 - Accessory Devices for Pressurized Metered Dose Inhalers
- Dry Powder Inhalers
 - Types of Dry Powder Inhalers
 - Factors Affecting Dry Powder Inhaler Performance and Drug Delivery

Selecting an Aerosol Device

Clinical Application of Aerosol Delivery Devices

- Recommendations Based on Clinical Evidence
 - Aerosol Delivery of Short-Acting β_2 Agonists in the Emergency Department

- Aerosol Delivery of Short-Acting β_2 Agonists in the Hospital
- Intermittent Versus Continuous Nebulizer Delivery of β_2 Agonists
- Aerosol Delivery of β_2 Agonists to Patients Receiving Mechanical Ventilation
- Aerosol Delivery of Short-Acting β_2 Agonists for Asthma in the Outpatient Setting
- Delivery of Inhaled Corticosteroids for Asthma
- Delivery of β_2 Agonists and Anticholinergic Agents for Chronic Obstructive Pulmonary Disease
- Factors to Consider

- Lung Deposition and Loss Patterns With Traditional Aerosol Devices

- Equivalent Doses Among Device Types

- Lung Deposition With Newer Aerosol Devices

- Clinical Equivalence of Metered Dose Inhalers and Nebulizers

- Age Guidelines for Use of Aerosol Devices

- Patient–Device Interface

- Administration by Intermittent Positive-Pressure Breathing

- Face Mask and Blow-by Administration

- Mechanical Ventilation Administration

- Adjunct Systems for Aerosol Therapy

- Technological Adjuncts for Aerosol Therapy

- Recommendations for the COVID-19 Pandemic

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to administration of aerosol agents
2. Define *aerosol therapy*
3. Select an appropriate aerosol medication nebulizer on the basis of particle size distributions
4. Discuss aerosol particle size and deposition in the lungs
5. Differentiate between the types of aerosol devices
6. Describe the clinical applications of aerosol devices
7. Recommend the use of various aerosol devices

KEY TERMS AND DEFINITIONS

Aerodynamic diameter of a particle Diameter of a unit-density (1 g/cc) spherical particle having the same terminal settling velocity as the measured particle.

Aerosol Suspension of liquid or solid particles 0.001 to 100 micrometers (μm) in diameter in a carrier gas.

Aerosol therapy Delivery of aerosol particles to the lungs.

Cascade impactor Device that uses multiple steps in determining size of aerosol particles.

Chlorofluorocarbon (CFC) Liquefied gas (e.g., Freon) propellant used to administer medication from a metered dose inhaler (MDI).

Dead volume Amount of solution that remains in the reservoir of a small-volume nebulizer once sputtering begins, causing a decrease in aerosolization.

Deposition Process of particles depositing out of suspension to remain in the lung.

Heterodisperse In reference to the size of particles in an aerosol, meaning the particles are of different sizes.

Hydrofluoroalkane (HFA) Nontoxic liquefied gas propellant used to administer medication from an MDI.

In vitro Mechanically simulating the clinical setting; testing in a laboratory.

In vivo Testing done on animals or humans; clinical testing.

Monodisperse In reference to the size of particles in an aerosol, meaning all particles being the same size.

Nebulizer Device used for making a fine spray or mist, also known as an *aerosol generator*.

Penetration Refers to the depth within the lung reached by particles.

Polydisperse In reference to the size of particles in an aerosol, meaning many different particle sizes.

Reservoir device Global term describing or referring to extension, auxiliary, or add-on devices attached to MDIs for administration. This term can include “spacer” and “valved holding chamber” (defined subsequently).

Spacer Simple tube or extension device with no one-way valves to contain the aerosol cloud; its purpose is simply to extend the MDI spray away from the mouth.

Stability Describing the tendency of aerosol particles to remain in suspension.

Valved holding chamber Spacer device with the addition of a one-way valve to contain and hold the aerosol cloud until inspiration occurs.

Aerosol therapy refers to the delivery of aerosol particles to the respiratory tract. At the present time, there are three main uses of aerosol therapy in respiratory care:

1. Humidification of dry inspired gases by using bland aerosols
2. Improved mobilization and clearance of respiratory secretions, including sputum induction, by using bland aerosols of water and hypertonic or hypotonic saline
3. Delivery of aerosolized drugs to the respiratory tract

This chapter presents information on delivery of aerosolized drugs to the respiratory tract. As outlined in [Chapter 2](#), the first prerequisite for a drug to exert a therapeutic effect at the target organ is an effective dosage form and route of administration for the target organ. Aerosol generation and delivery to the lung is a complex topic. Development of the technology and the scientific basis of inhaled aerosol administration is ongoing. This chapter reviews physical principles of aerosol delivery to the airways and aerosol-generating devices for inhalation of drugs. Research findings on aerosol delivery devices and methods of administration are summarized. The general advantages supporting the use of aerosolized drug therapy in respiratory care and the disadvantages with this method of drug delivery are summarized in [Box 3.1](#).

Physical Principles of Inhaled Aerosol Drugs

KEY POINT

An *aerosol* is a suspension of solid or liquid particles whose *deposition* in the respiratory tract is determined by *inertial impaction*, *gravitational settling* (*sedimentation*), and, perhaps less importantly, *diffusion* (*brownian motion*).

The term *aerosol* has been used since the beginning of the twentieth century; however, inhaled agents used for medicinal purposes date back 4000 years ago.¹ The following definitions apply to inhaled therapeutic aerosols:

Aerosol: Suspension of liquid or solid particles between 0.001 and 100 micrometers (μm) in diameter in a carrier gas.² For pulmonary diagnostic and therapeutic applications, the particle size range of interest is 1 to 10 μm . Particles in this size range are small enough to exist as a suspension and to enter the lung

• BOX 3.1 Advantages and Disadvantages Seen With Aerosol Delivery of Drugs

Advantages

- Aerosol doses are smaller than doses for systemic treatment.
- Onset of drug action is rapid.
- Drug delivery is targeted to the respiratory system for local pulmonary effect.
- Systemic side effects are fewer and less severe than with oral or parenteral therapy.
- Inhaled drug therapy is painless and relatively convenient.
- The lung provides a portal to the body for inhaled aerosol agents intended for systemic effect (e.g., pain control, insulin).

Disadvantages

- Numerous variables affect dose of aerosol drug delivered to airways.
- Dose estimation and dose reproducibility are inconsistent.
- Many patients have difficulty in coordinating hand action and breathing with metered dose inhalers (MDIs).
- Many physicians, nurses, and therapists lack knowledge of device use and administration protocols.
- Standardized technical information on aerosol-producing devices is lacking for practitioners and patients.
- Numerous device types and variability of use are confusing to patients and practitioners.

and large enough to deposit and contain the required amount of an agent.^{3,4}

Stability: Describing the tendency of aerosol particles to remain in suspension.

Penetration: Referring to the depth within the lung reached by particles.

Deposition: Describing the process by which particles deposit out of suspension to remain in the lung.

Aerosol-generating devices for orally inhaled drugs have typically had an efficiency of 10% to 15%; that is, only 10% to 15% of a given dose from a device usually reaches the lower respiratory tract, regardless of the device type. Newer aerosol-generating devices are proving to be exceptions to this lack of efficiency, with 30% to 50% or more of the dose reaching the lungs.

Aerosol Particle Size Distributions

KEY POINT

A major factor in lung penetration by aerosols is particle size, which is best characterized by the *mass median aerodynamic diameter (MMAD)* for inhaled drugs because particle mass is a function of the third power of the particle radius. The particle size of interest for pulmonary applications is in the range of 1 to 10 μm , and the fine particle fraction (FPF) is considered to include particles less than 5 μm in size.

Aerosol particles produced for inhalation into the lungs via inhalant devices, such as metered dose inhalers (MDIs), small volume nebulizers (SVNs), and dry powder inhalers (DPIs), include a range of sizes (**polydisperse** or **heterodisperse**) rather than a single size (**monodisperse**).

Count mode: Most frequently occurring particle size in the distribution.

Count median diameter (CMD): Particle size above and below which 50% of the particles are found (i.e., the size that evenly divides the number of particles in the distribution).

Mass median diameter (MMD) or MMAD: Particle size above and below which 50% of the mass of the particles are found (i.e., the size that evenly divides the mass of the particles in the distribution).

Geometric standard deviation (GSD): Measure of the dispersion of a distribution (i.e., the scattering of values from the average), calculated as the ratio of particle size below which 84% of the particles occur to the particle size below which 50% occur, in a log-normal distribution. This ratio determines how spread out the particles are in relationship to their size.

The MMD, or MMAD, indicates where the mass of drug is centered in a distribution of particle sizes. Aerosol particles are three-dimensional and have volume. Aerosol particles are assumed to be roughly spherical, and the relationship of volume (or mass, if all particles have equal densities) to diameter in a sphere is given by the following formula:

$$V = \left(\frac{4}{3}\right)\pi r^3$$

$V = \text{volume}; r = \text{radius}$

The volume increases or decreases as the third power of the radius of the particle, as seen in the preceding formula. As a result, the bulk of drug mass is centered in the larger particle sizes. Because it is the mass of the drug entering the lung on which the therapeutic effect is based, it is necessary to know where the mass is centered in a range of particle sizes to know whether that distribution will be efficient for penetration into the respiratory tract and delivery of an adequate dose.

Example

Two hypothetical SVNs, A and B, have the following specifications from the manufacturer:

A	B
CMD = 1.9 μm	CMD = 1.7 μm
MMAD = 3.4 μm	MMAD = 7.9 μm
GSD = 1.2	GSD = 1.6

Although nebulizer B has a smaller CMD compared with nebulizer A, which appears to indicate that it gives smaller particles, it is evident from the respective MMADs that nebulizer B has more particles in a larger size range ($\geq 5 \mu\text{m}$) compared with nebulizer A. Nebulizer A produces particles whose mass centers within a lower size range (1–5 μm) and would be the better nebulizer for treatment of the lower respiratory tract.

Inspect aerosol products for their MMAD because this is the best way to determine whether the nebulizer would be better suited for the upper or lower airway.

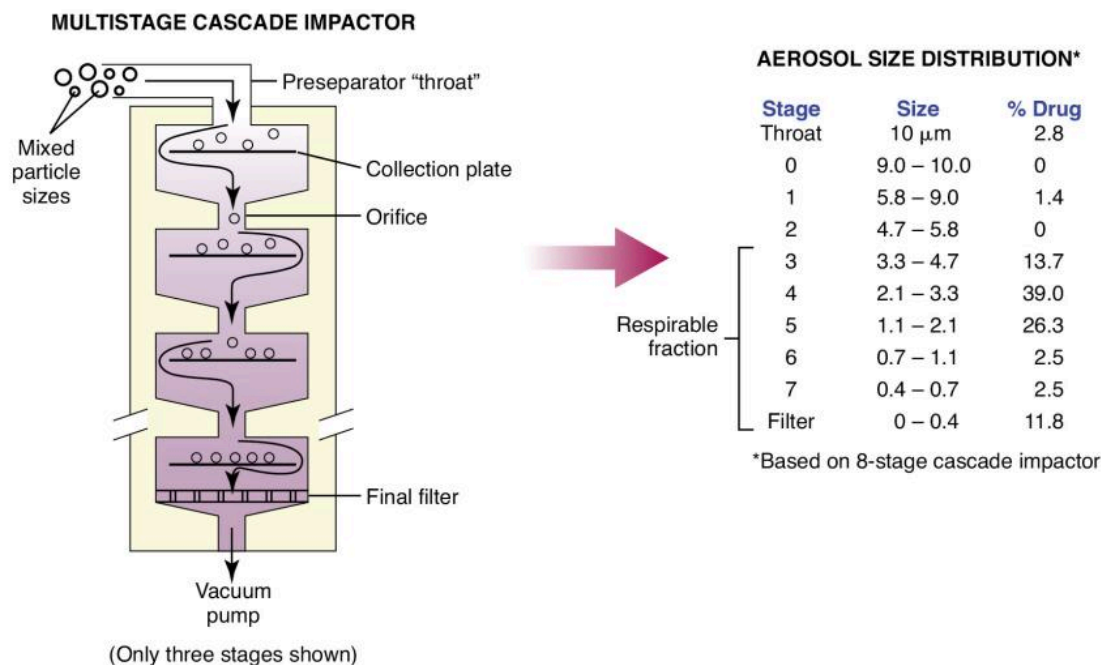
Aerosol generators should be characterized by using the MMD for the center of distribution and either the standard deviation or GSD to indicate the range of variability of particle size.

Measurement of Particle Size Distributions

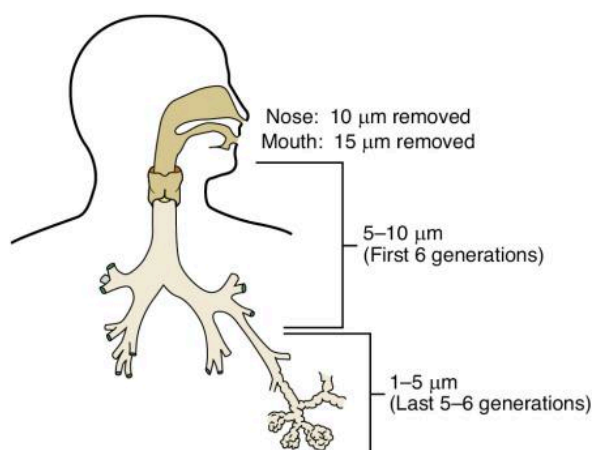
Several physical methods are used to measure aerosol particle size distributions, including *cascade impaction* and, less commonly, *laser scattering*. The **cascade impactor** measures what is termed the *aerodynamic diameter of aerosols* because the measurement is based on the aerodynamic behavior (sedimentation velocity and impaction characteristics) of the particles in the cascade impactor. Measuring particle size with the *laser-scattering method*, the instrument determines the relationship between the intensity and the angle of light scattered from a particle, then calculates the particle size based on the Mie-scattering theory. The **aerodynamic diameter of a particle** is the diameter of a unit-density (1 g/cc) spherical particle having the same terminal settling velocity as the measured particle.^{4,5}

The principle by which a cascade impactor measures the particle size distribution of an aerosol cloud is illustrated in a simplified diagram in Fig. 3.1. The *cascade impactor* consists of a series of stages, each of which has progressively smaller orifices through which the aerosol particles must pass. A constant flow draws the particles through the stages. The largest particles are collected on the first stage, and particles not impacting out at this stage move on to the subsequent stages with smaller orifices in the airstream. By means of successively smaller filtration stages, the particles are separated, or *fractionated*, on the basis of size. Any particles leaving the last stage are collected on a final filter.

The amount of aerosol on each stage is measured by weight or, preferably, by spectrophotometry or high-performance liquid chromatography (HPLC). HPLC is considered the most sensitive technique for quantifying the amount of aerosol on each stage. Because each stage is calibrated for a unit-density sphere of specific diameter, the distribution of aerodynamic diameters can be calculated as the percentage of a drug on each stage. The MMAD can be determined as the particle size dividing the drug in half. Sources of error in aerodynamic measures include particle bounce, interstage impaction, possible fragmentation of particles, and particle evaporation or condensation.⁵ In addition, **in vitro** methods (mechanically simulating the clinical setting within a laboratory) of aerosol measurement may not reflect conditions in the human lung, such as temperature, humidity, inspiratory flow rates, and exhalation phase. Dolovich⁶ reviewed in vitro measures used with MDI and auxiliary devices. Feddah et al.⁷ found that MDI formulations did better in vitro compared with DPI formulations with respect to inhaled doses. The same method of aerosol characterization is not useful or accurate for different methods of aerosol production because of differences in the physical nature of their generation. To determine aerosol particle behavior in animals or humans, **in vivo** methods would be studied.



• **Fig. 3.1** The principle of aerodynamic particle size measurement, using multistage cascade impaction. A series of successively smaller orifices and collection plates separate large and smaller particle sizes. Drug amounts (% Drug) shown are actual measures of particle sizes for a sample of albuterol (Ventolin) through a Volumatic reservoir. (Data from J. P. Mitchell, Trudell Medical International Aerosol Laboratory, London, Ontario, Canada.)



• **Fig. 3.2** Effect of aerosol particle size on area of preferential deposition within the airway.

Particle Size and Lung Deposition

A major factor influencing aerosol deposition in the lung is particle size. The effect of particle size on deposition in the respiratory tract is illustrated in Fig. 3.2.

The upper airway (nose and mouth) is efficient in filtering particulate matter, so generally, there is 100% deposition in the nose and mouth of particles larger than 10 to 15 μm . Particles sized from 5 to 10 μm tend to deposit out in the upper airways and the early airway generations, whereas particles from 1 to 5 μm in size have a greater probability of reaching the lower respiratory tract (from the trachea to the lung periphery). Larger or coarser aerosol particles ($\geq 5 \mu\text{m}$ in diameter) may be useful for treating the upper airway (nasopharynx and oropharynx). It is impossible to specify

exactly where a given size of particle will deposit in the lung. Particle deposition is a function of several mechanisms, including the breathing pattern. For example, tables are often created listing the percentage of droplets of a given size that will deposit in the lung at each bronchial level.⁸ Hoffman⁹ observed that optimal deposition in the normal human lung is achieved for particles of 3 μm inhaled with low inspiratory flows of less than 1 L/sec (≤ 60 L/min) and tidal volumes of 1 L; total lung deposition is divided almost equally throughout the 23 lung generations.

Fine Particle Fraction

The labels *respirable fraction* and *respirable dose* were used previously to refer to the percentage or fraction of aerosol drug mass in a particle size range with a high probability of penetrating into the lower respiratory tract. These generally have been considered to be in the particle size range of less than 5 to 6 μm . There is rarely an absolute correspondence of lower respiratory tract deposition to this particle size range because of age, disease, and breathing patterns, all of which can affect lung deposition. The more descriptive terms *fine particle fraction (FPF)* and *fine particle dose (FPD)* were proposed for use in place of respirable fraction and respirable dose.¹⁰ There was no consensus regarding what size fraction represents the FPF. These terms may be restricted to particles 1 to 3 μm , rather than particles less than 5 to 6 μm .

Particle Size and Therapeutic Effect

Because the respiratory tract apparently functions as a progressive filter of successively smaller particles from the upper airway to the periphery, specific areas of the respiratory tract may be targeted by various aerosol particle sizes. On the basis of the preceding considerations, the respiratory tract might be segmented according to particle size ranges, as discussed below.

Particles greater than 10 μm . Particles that are greater than 10 μm are useful to treat the nasopharyngeal and oropharyngeal regions. An example is a nasal spray for perennial rhinitis, such as a corticosteroid.

Particles 5 to 10 μm . Particles 5 to 10 μm may shift deposition to the more central airways, although significant oropharyngeal deposition is expected. An example is a nasal spray, but there is no one standard device that creates this specific particle size. Most aerosol devices use a smaller particle size (discussed below).

Particles 2 to 5 μm . As particle size decreases to less than 5 μm , deposition shifts from the oropharynx and large airways to the overall lower respiratory tract (large airways to periphery).¹¹ This size range is considered useful for the bronchoactive aerosols currently in use. For example, β -adrenergic receptors have been identified throughout the airway, but with greater density in bronchioles. Clay et al.¹² showed greater improvement in mid-maximal expiratory flow rates among patients using a β -adrenergic bronchodilator with an MMAD of 1.8 μm than with an MMAD of 4.6 or 10.3 μm . This finding was confirmed subsequently by Johnson et al.,¹³ who found a greater response to the β -adrenergic bronchodilator albuterol (see Chapter 6) with an MMD of 3.3 μm compared with 7.7 μm . Leach¹⁴ found similar results with a **chlorofluorocarbon (CFC)**-MDI of albuterol, where particles averaged 3.5 to 4.0 μm ; however, when testing a **hydrofluoroalkane (HFA)**-MDI, particle size decreased to an average of 1.1 μm . In contrast, cholinergic receptors are numerous in proximal bronchial smooth muscle but rare in distal bronchioles.¹⁵

Particles 0.8 to 3.0 μm . Increased delivery of an aerosol to the lung parenchyma, including the terminal airways and alveolar region, can be achieved with particles less than 3 μm .¹¹ An MMAD of 1 to 2 μm is suggested for peripheral deposition of the anti-infective drug pentamidine to minimize deposition in and irritation of larger airways and to maximize intraalveolar deposition.¹⁶ However, with the introduction of HFA-MDIs, a finer particle size is seen.¹⁴

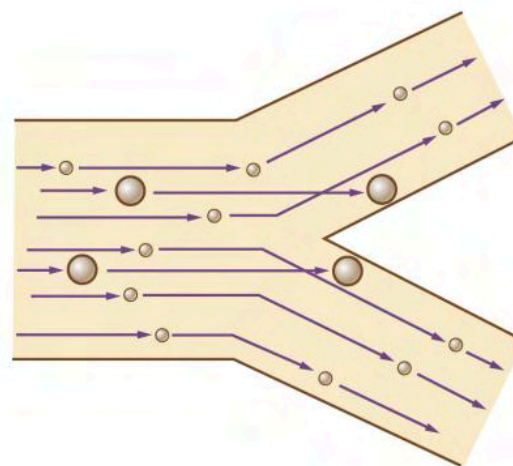
Mechanisms of Deposition

Three physical mechanisms usually are considered for aerosol particle deposition in the human lung:

1. Inertial impaction
2. Gravitational settling (sedimentation)
3. Diffusion (brownian motion).

Inertial Impaction. As shown in Fig. 3.3, *inertial impaction* is a function of particle size (mass) and velocity and increases with larger size and higher velocities. In the upper airway and early bronchial generations, particle velocity is highest, airflow tends to be turbulent, and total cross-sectional area of the airway is smallest. These factors favor inertial impaction for larger, fast-moving particles on the airway wall, especially at airway bifurcations. Deposition by inertial impaction is expected to occur in the first 10 airway generations.⁴

Gravitational Settling. *Gravitational settling*, or *sedimentation*, is a function of particle size and time. Settling is greater for larger particles with slow velocities, which are under the influence of gravity. As particles small enough to escape inertial impaction in earlier airway generations reach the periphery, velocity probably slows, and airflow is less turbulent. There is also a shorter distance to the airway wall in smaller, peripheral airways, favoring impaction resulting from settling (Fig. 3.4). The probability of deposition by sedimentation is highest in the last five or six airway generations.⁴ Because the process of sedimentation is time



• **Fig. 3.3** Inertial impaction of large particles, the masses of which tend to maintain their motion in straight lines. As airway direction changes, the particles are deposited on nearby walls. Smaller particles are carried around corners by the airstream and fall out less readily. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. [2017]. *Egan's Fundamentals of Respiratory Care* [11th ed.]. St. Louis, Missouri: Mosby.)

dependent, the end-inspiratory breath hold should maximize deposition in the periphery. The rate of settling is proportional to the square of the particle size. For a 5- μm -diameter particle, the settling rate is reported to be 0.7 mm/sec.¹⁷ The use of a breath hold can increase settling of particles; however, depending on particle size, a particle may not fall out of suspension.

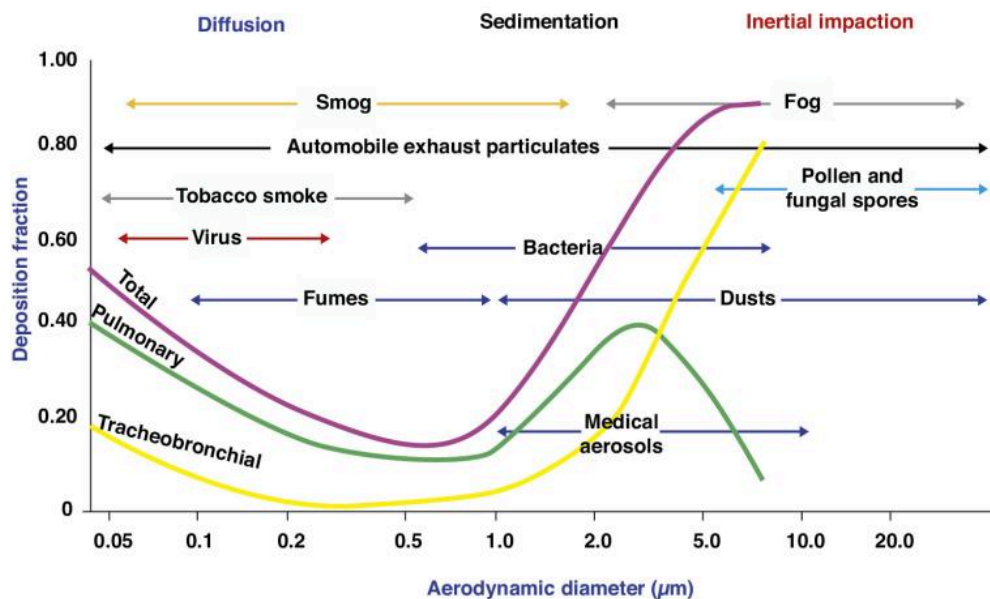
Diffusion (Brownian Motion). *Diffusion (brownian motion)* affects particles less than 1 μm in diameter and is a function of time and random molecular motion. Particles 0.1 to 1.0 μm in size may remain suspended or even exhaled because the time required to diffuse to the airway surface tends to be greater than the inspiratory time of a normal breath.¹⁸ The importance of diffusion for lung deposition of therapeutic aerosols is debatable because the size range involved contains very little drug mass but gives great stability. Fig. 3.5 shows the relationship between particle size and aerosol deposition in the respiratory tract.

CLINICAL CONNECTION

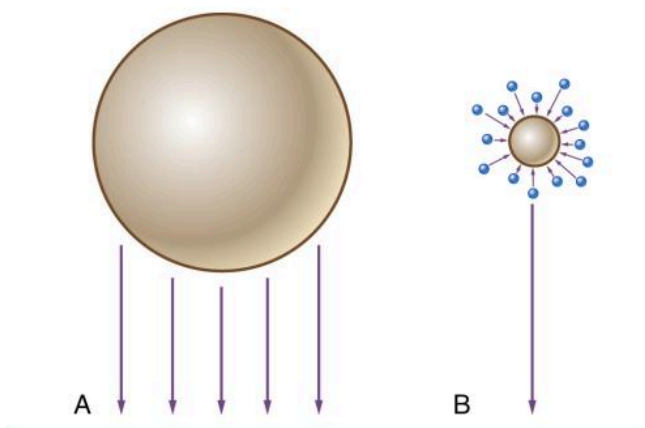
Aerosol particles released in the atmosphere will increase in size as they make their way into the airway as a result of increase in temperature and humidity.

Effect of Temperature and Humidity

Prediction of particle deposition with therapeutic aerosols is complicated further by the fact that the aerosol is generated under relatively dry ambient conditions and then taken into the airway, where temperature and humidity rapidly increase to saturation at 37°C. Inhaled aerosol drugs are not only heterodisperse in size but are also *hygroscopic* (i.e., readily absorbing moisture). Between ambient and BTPS (body temperature, ambient pressure, saturated) conditions, the MMAD of cromolyn sodium powder particles from an MDI increases from 2.31 to 3.02 μm .^{19,20} Williams et al. measured approximately 20% to 90% reduced drug delivery from heated humidity in an endotracheal tube in vitro model with a closed suction catheter connected to a ventilator.²¹



• **Fig. 3.4** Range of particle size for common aerosols in the environment and the influence of inertial impactions, sedimentation, and diffusion. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. [2017]. *Egan's Fundamentals of Respiratory Care* [11th ed.]. St. Louis, Missouri: Mosby.)



• **Fig. 3.5** Effect of mass on particle size. Large particles (A) are more susceptible to the force of gravity than smaller particles (B), which are more affected by the bombardment of molecules deposited by diffusion. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. [2017]. *Egan's Fundamentals of Respiratory Care* [11th ed.]. St. Louis, Missouri: Mosby.)

Aerosol Generators for Drug Delivery

KEY POINT

Common devices for the delivery of inhaled aerosol drugs include small volume nebulizers (SVNs), pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). *Reservoir devices*, such as spacers and holding chambers, can reduce oropharyngeal deposition of a drug and simplify hand-breathing coordination with pMDIs. Proper use of these aerosol-generating devices is necessary to ensure adequate lung delivery, and correct use should be understood by practitioners. Traditional aerosol-generating devices all deliver about 10% to 15% of the dose produced to the lung, although different types of devices vary in their loss patterns.

Lung deposition depends on various factors, such as the aerosol generator, the patient, the drug, and the disease. Depending on the type of SVN used, most of the drug loss with an SVN

occurs in the device, whereas the main drug loss with a pressurized metered dose inhaler (pMDI) and DPI is in the oropharyngeal airways. Adding a reservoir device to a pMDI or using a nonelectrostatic valved holding chamber shifts loss from the throat to the reservoir and increases aerosol deposition in the lungs. Lung deposition may range from 1% to 40% with aerosol generators.^{22–27} Fig. 3.6 provides the percentages of drug deposition for different aerosol generators, showing that oropharyngeal loss, device loss, and exhalation and ambient loss differ among aerosol device types, as do lung doses.

The overall efficiency in lung deposition of 10% to 15% of the total drug dose is not significantly better than with most pMDIs or DPIs used clinically in the past, as discussed subsequently in the section on clinical application and equivalence of various devices. Nebulizers as well as MDIs and DPIs are undergoing an evolutionary transition toward greater efficiency.

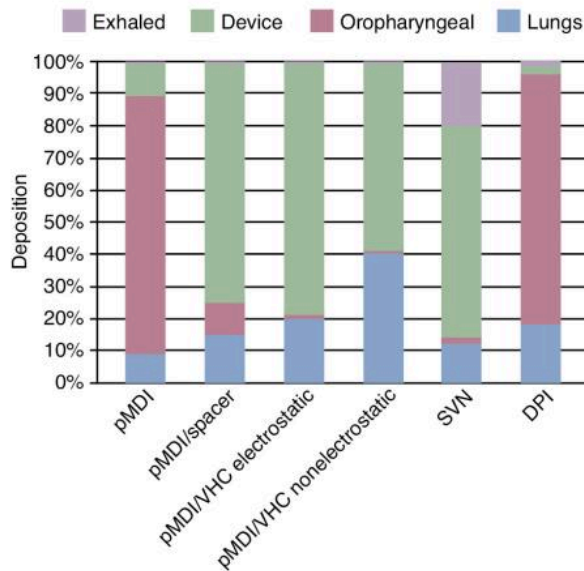
Nebulizers

The term **nebulizer** encompasses various devices that operate on different physical principles to generate an aerosol from a drug solution. The SVN is a type of aerosol generator that converts liquid drug solutions or suspensions into aerosol. SVNs are powered by compressed gas (air or oxygen), a compressor, or an electrically powered device.²⁷ Because jet nebulizers are often used with infants or with patients in acute respiratory distress, slow breathing and an inspiratory pause may not be feasible or obtainable. One of the main advantages of SVNs is that dose delivery occurs over 60 to 90 breaths, rather than in one or two inhalations. A single ineffective breath does not destroy the efficacy of the treatment. Box 3.2 summarizes the advantages and disadvantages of SVNs.

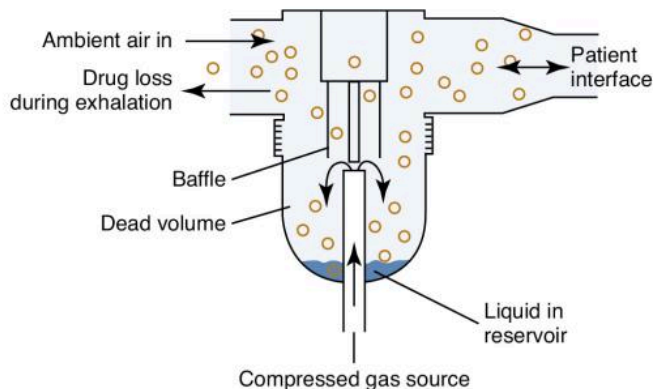
Types of Small Volume Nebulizers

SVNs can be classified into three categories²⁷:

1. Jet (pneumatic) nebulizers
2. Mesh nebulizers
3. Ultrasonic nebulizers (USNs)



• **Fig. 3.6** Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath. *DPI*, Dry powder inhaler; *pMDI*, pressurized metered dose inhaler; *SVN*, small volume nebulizer; *VHC*, valved holding chamber. (From Gardenhire, D. S., Burnett, D., Strickland, S., & Myers, T. R. [2018]. *A Guide to Aerosol Delivery Devices for Respiratory Therapists* [4th ed.]. Irving, Texas: American Association for Respiratory Care.)



• **Fig. 3.7** Schematic of a small volume jet nebulizer. (Modified from Cairo, J. M. [2014]. *Mosby's Respiratory Care Equipment* [9th ed.]. St. Louis, Missouri: Elsevier.)

Jet (Pneumatic) Nebulizers. Jet (pneumatic) nebulizers are small-reservoir, gas-powered (pneumatic) aerosol generators, also referred to as *handheld nebulizers*, *updraft nebulizers*, or *unit-dose nebulizers*. The traditional jet nebulizer is commonly used and exhibits a large amount of drug wastage, especially within the device itself; see Fig. 3.7 for a generic illustration. Jet nebulizers use a jet-shearing principle for creation of an aerosol from the drug solution. An external source of compressed gas is directed through a narrow orifice inside the reservoir cup. The expanding gas creates a localized negative pressure, drawing the drug solution up feeder tubes. As the liquid enters the gas stream, droplets are formed from gas turbulence and impaction on baffles. Smaller particle sizes are emitted after the baffling process. Larger liquid particles are recirculated back to the reservoir. There is significant evaporation of the aqueous solution with gas-powered nebulization.

• BOX 3.2 Advantages and Disadvantages of Small Volume Nebulizers

Advantages

- Ability to aerosolize many drug solutions.
- Ability to aerosolize drug mixtures (i.e., more than one drug) with suitable testing of drug activity.
- Minimal cooperation or coordination required for inhalation.
- Useful in very young or very old patients, debilitated patients, and patients in acute distress.
- Effective with low inspiratory flows or volumes.
- Normal breathing pattern can be used, and inspiratory pause (breath hold) not required for efficacy.
- Drug concentrations and dose can be modified, if desired.

Disadvantages

- Equipment required for use is expensive and cumbersome.
- Treatment times are somewhat lengthy, ranging from 5 to 25 minutes, depending on the type of small volume nebulizer used for aerosol drug delivery.
- There is variability in performance characteristics among different types, brands, and models.
- Contamination is possible with inadequate cleaning.
- Assembly and cleaning are required.
- Wet, cold spray occurs with mask delivery.
- Aerosol drug administration with a face mask may inadvertently deposit in the eyes, resulting in eye irritation.
- Power source (compressed gas, battery, or electricity) is needed for aerosol drug administration.

Nebulizer temperatures can fall from ambient to approximately 10°C within minutes because of the latent heat of vaporization. With evaporation and constant recirculation, drug solute becomes increasingly concentrated, up to 150% to 300% of the original concentration.²⁸

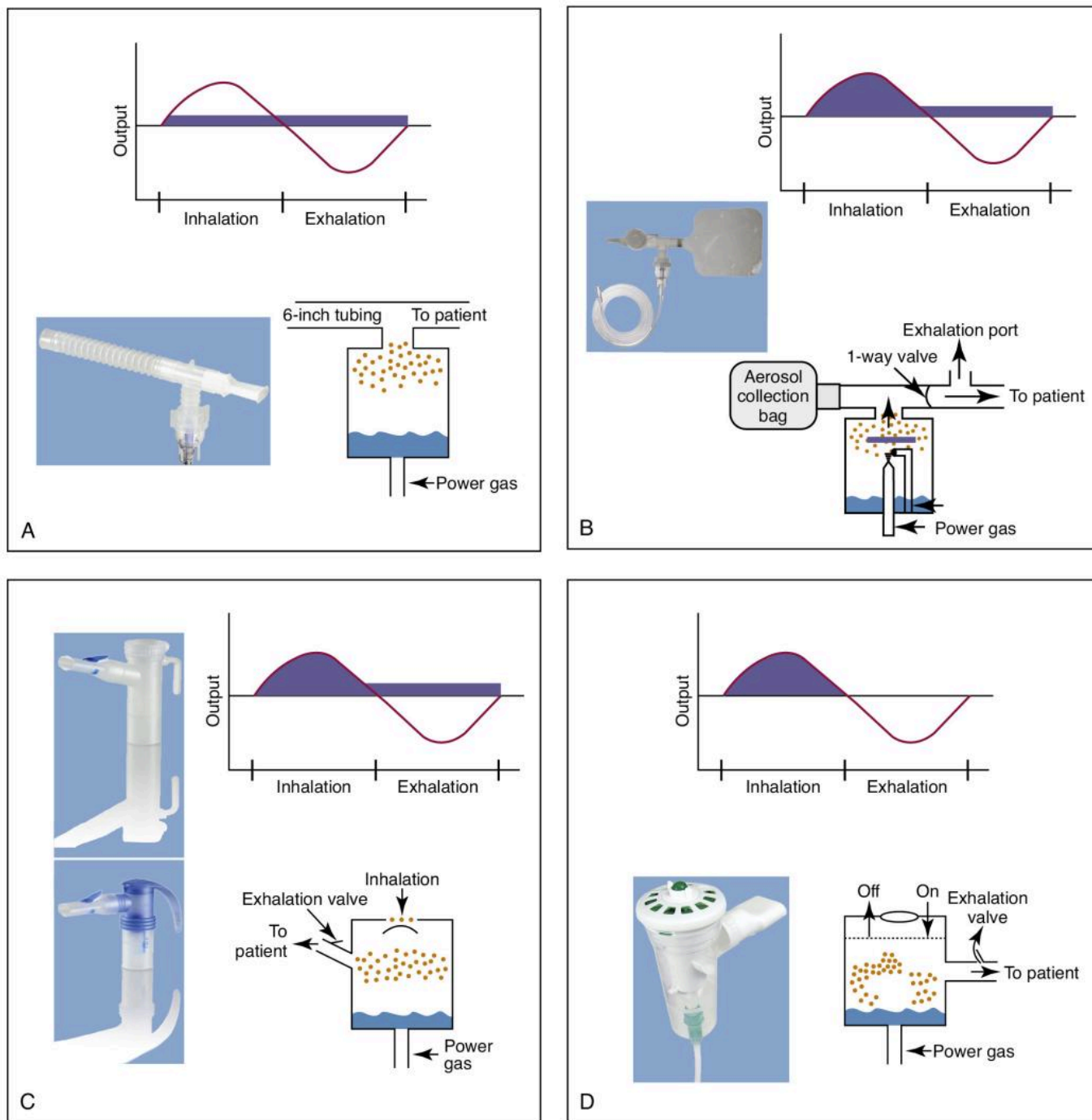
Pneumatic jet nebulizers have been conceptualized into four categories^{27–29}:

1. Jet nebulizer with reservoir tube
2. Jet nebulizer with collection bag/elastomeric ball
3. Breath-enhanced jet nebulizer
4. Breath-actuated jet nebulizer

Fig. 3.8 illustrates the types of pneumatic jet nebulizers and their aerosol outputs.

Jet Nebulizer With Reservoir Tube. A jet nebulizer with reservoir tube is the traditional, least expensive, and most widely used nebulizer in which aerosol is produced constantly during inspiration, expiration, and breath hold.^{28,30} Although the addition of 6 inches of reservoir tubing reduces the release of aerosol to ambient air during exhalation and breath hold, it does not eliminate ambient contamination. These nebulizers provide a low percentage of the dose to the patient and have been considered to be inefficient because only 10% to 20% of the emitted dose is inhaled. The Misty-neb (Cardinal Health, Dublin, Ohio) and the Neb U mist (Hudson RCI, Durham, North Carolina) are examples of this type of jet nebulizer.

Jet Nebulizer With Collection Bag or Elastomeric Ball. A jet nebulizer with collection bag produces aerosol by continuously filling a collection bag, and no aerosol is lost during expiration because of the one-way inspiratory valve between the nebulizer and the mouthpiece. Through an inspiratory valve, the patient inhales aerosol from the collection bag and exhales to the atmosphere

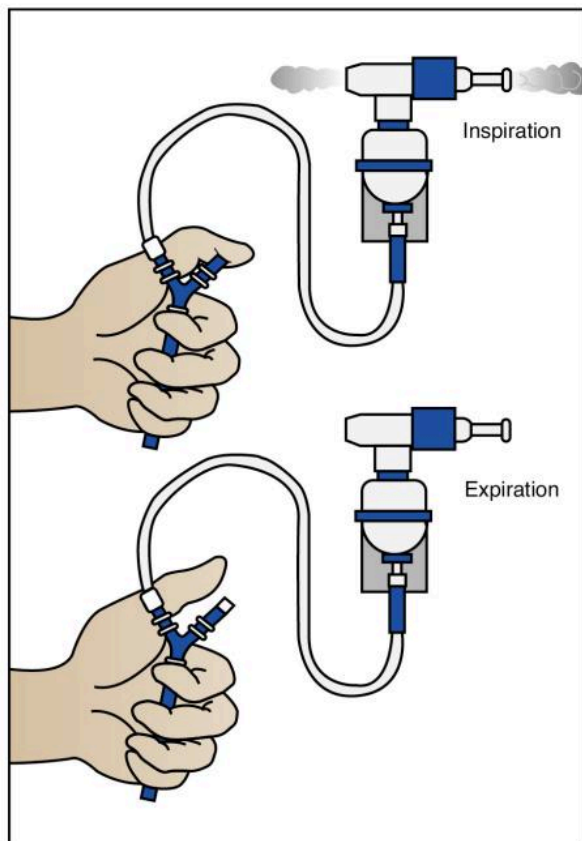


• **Fig. 3.8** Different types of pneumatic jet nebulizer designs and their aerosol output, indicated by shaded area. **A**, Pneumatic jet nebulizer with reservoir tube. **B**, Jet nebulizer with collection bag. **C**, Breath-enhanced jet nebulizer. **D**, Breath-actuated jet nebulizer. (Modified from Gardenhire, D. S., Burnett, D., Strickland, S., & Myers, T. R. [2018]. *A Guide to Aerosol Delivery Devices for Respiratory Therapists* [4th ed.]. Irving, Texas: American Association for Respiratory Care.); **A inset**, Courtesy DeVilbiss Healthcare, Somerset, Pennsylvania; **B inset**, Courtesy Westmed, Inc., Tucson, Arizona; **C inset**, Courtesy PARI Respiratory Equipment, Inc., Midlothian, Virginia; **D inset**, AeroEclipse II Breath Actuated Nebulizer, Courtesy Trudell Medical International, London, Ontario, Canada.)

through the exhalation port placed between the one-way inspiratory valve and the mouthpiece.^{27,30} The Circulaire II (SunMed, Grand Rapids, Michigan) is one model of a jet nebulizer with collection bag. The Circulaire Hybrid (SunMed) contains a soft elastomeric ball as the reservoir. The ball is simple to remove and easily washed and dried, which facilitates home use.

Breath-Enhanced Jet Nebulizer. Breath-enhanced jet nebulizers allow more aerosol release during inspiration with decreased output during exhalation or breath hold through two one-way valves used to prevent the loss of aerosol to the environment. Although aerosol is produced during inspiration and expiration, the inspiratory valve opens and gas vents through the nebulizer

only when the patient inhales. Expired gas is routed through a one-way valve in the mouthpiece; aerosol is contained in the reservoir and there is reduced ambient loss. Pari LC Plus (PARI Respiratory Equipment, Inc., Midlothian, Virginia), NebuTech (Salter Labs, Arvin, California), and Ventstream Pro (Phillips Healthcare, Andover, Massachusetts) are examples of breath-enhanced nebulizers.



• **Fig. 3.9** Schematic illustration of the function of a manual breath-actuated jet nebulizer. Use of a finger control regulates production during inspiration and expiration. (From Cairo, J. M. [2014]. *Mosby's Respiratory Care Equipment* [9th ed.]. St. Louis, Missouri: Elsevier.)

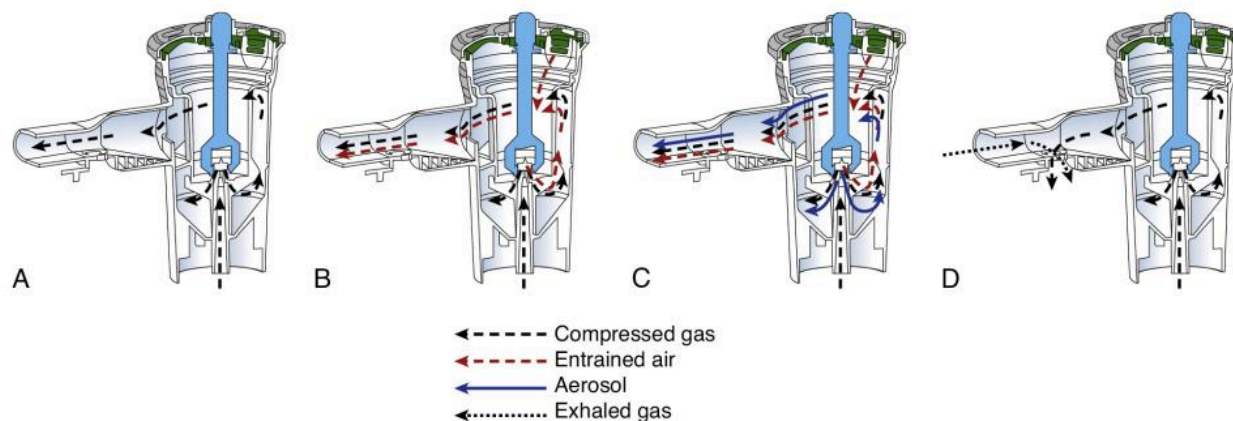
Breath-Actuated Jet Nebulizer. Breath-actuated jet nebulizers release aerosol only during inspiration because they are designed to increase aerosol drug delivery to patients by reducing loss of medication during expiration. Although breath-actuated nebulizers increase the inhaled dose by more than threefold, their efficiency is achieved by an increase in dosing time.³⁰ The two types of breath-actuated nebulizers are²⁷:

1. Manual breath-actuated jet nebulizers
2. Mechanical breath-actuated jet nebulizers

Manual Breath-Actuated Jet Nebulizer. Manual breath-actuated jet nebulizers represent the first generation of breath-actuated nebulizers, which regulate aerosol production during inspiration and expiration through use of a patient-controlled thumb port. In manual breath-actuated nebulizers, dose delivery occurs only during inspiration; the thumb control is blocked so that there is no nebulization during expiration. Releasing the thumb at the port pauses the nebulization. Even though this type of nebulizer reduces drug loss during expiration, they require good hand-breath coordination and significantly increase the treatment time.^{25–27} Fig. 3.9 illustrates the relationship of nebulizer generation with a manual breath-actuated jet nebulizer.

Mechanical Breath-Actuated Jet Nebulizer. Mechanical breath-actuated jet nebulizers have a breath-actuated valve that is triggered by patients creating an inspiratory force (Fig. 3.10). When the breath-actuated valve is triggered, aerosol is produced only during inspiration. This type of nebulizer eliminates the need for a collection bag or reservoir.^{27,30} The AeroEclipse II (Trudell Medical International, London, Ontario, Canada) is an example of a mechanical breath-actuated nebulizer. The AeroEclipse II is also available in a reusable nebulizer (R BAN; Trudell Medical International).

Mesh Nebulizers. Mesh nebulizers move the liquid formulations through a fine plate or mesh with multiple apertures (small holes) to generate aerosol. These nebulizers have no internal baffling mechanism and create aerosol by using the aperture plate or the ultrasonic horn. The diameter of the apertures determines the size of the particle generated. Mesh nebulizers do not require a gas source because they are powered by battery or electricity, and they leave very little dead volume (0.1–0.5 mL) in the nebulizer, so they are very efficient. There are two types of mesh nebulizers on the market^{25–27}:



• **Fig. 3.10** Schematic illustration of the function of a mechanical breath-actuated nebulizer. **A**, Before inhalation. **B**, Patient inhales, and actuator starts to move down. **C**, Negative pressure pulls the diaphragm down (with actuator moved down, sealing around the nozzle cover), producing aerosol. **D**, Patient exhales through valve in mouthpiece. As pressure increases, the diaphragm and actuator move up, stopping aerosol production. (Courtesy Trudell Medical International, London, Ontario, Canada.)

1. Active vibrating mesh nebulizers
2. Passive mesh nebulizers

Active Vibrating Mesh Nebulizer. Active vibrating mesh nebulizers (VMNs) have an aperture plate with greater than 1000 funnel-shaped holes on an electroformed sheet that is vibrated by a piezo-ceramic element that surrounds the aperture plate.^{25–27,31} The Aeroneb Solo, Ultra and Pro (Aerogen, Galway, Ireland) and eFlow (PARI Respiratory Equipment, Inc., Midlothian, Virginia) are examples of active VMNs (Fig. 3.11).

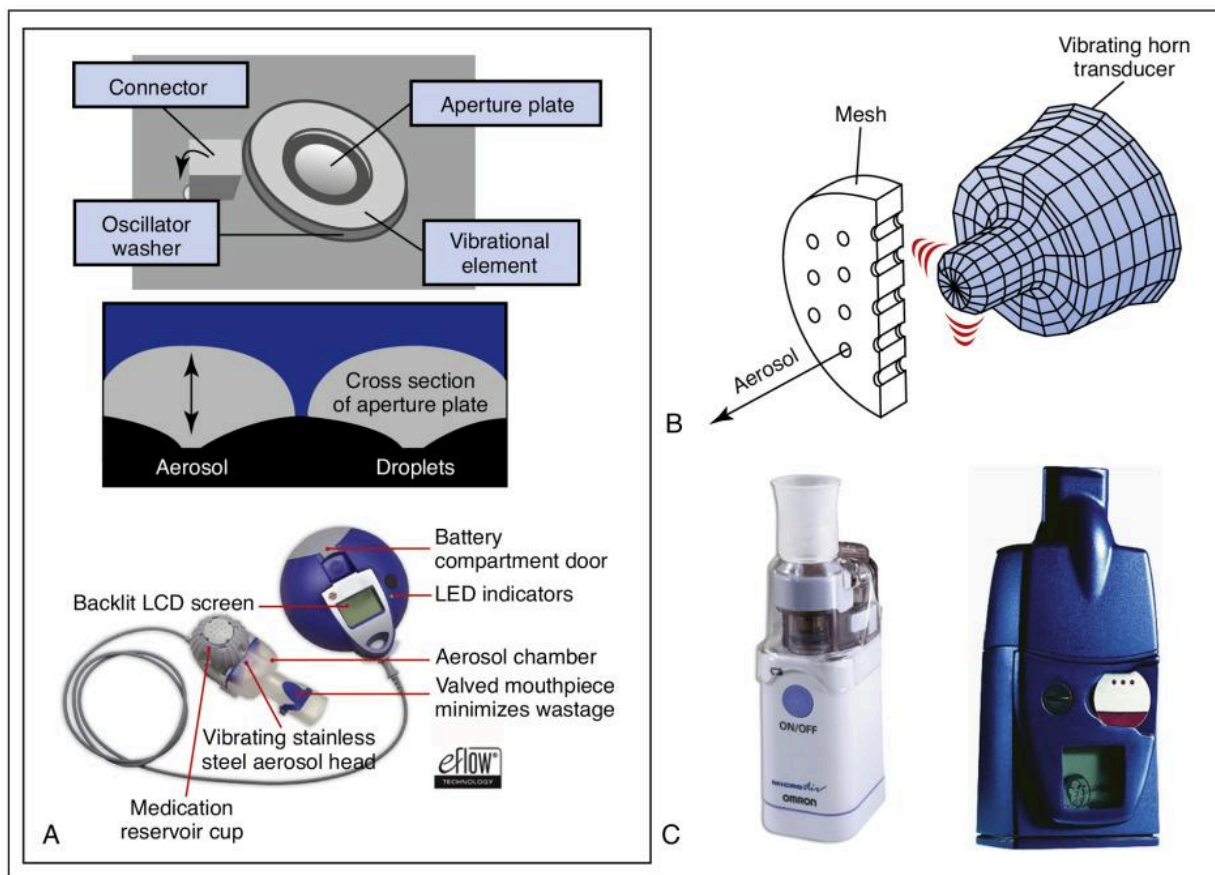
Passive Mesh Nebulizer. Passive mesh nebulizers use an ultrasonic horn to push fluid through the mesh. An example of passive mesh nebulizer is the adaptive aerosol delivery (AAD) system, such as the I-neb (Phillips Healthcare, Andover, Massachusetts). I-neb is a small, battery-operated, lightweight, and silent aerosol generator designed to deliver a precise and reproducible dose of drug. After aerosol is injected into the breath at the beginning of inhalation, the dosage of the drug is controlled through an AAD disk and specific metering chamber that delivers a preset volume ranging from 0.25 to 1.4 mL with a residual volume of about 0.1 mL^{25–27} (Fig. 3.12). In addition, the I-neb incorporates an AAD algorithm that pulses medication delivery into 50% to 80% of each inspiration based on a rolling average of the last three breaths. On successful delivery of the medication, the I-neb provides continuous audible and tactile feedback to the patient through a liquid crystal display.²⁷

Ultrasonic Nebulizers. USNs are electrically powered devices operating on the piezoelectric principle and capable of high

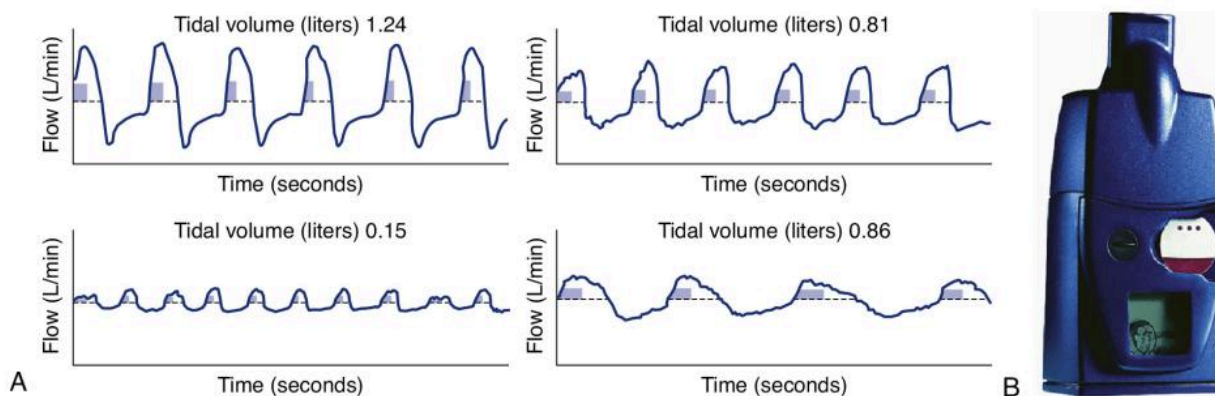
output. Particle sizes vary by brand. Fig. 3.13 is a generic illustration of a USN. Although these devices have not been used as routinely as other types (described below) for aerosolization of drugs, they have been reintroduced as small, portable units that can operate on direct current (DC) voltage. Such units have several advantages and some disadvantages, as listed in Box 3.3.

At the frequencies used in medical devices, there are several effects with the potential for altering drug activity of the nebulizer solution. Most of the energy produced during ultrasonic nebulization is dissipated as heat. Protein and other heat-sensitive (or *thermolabile*) formulations can be denatured by heat, especially if the melting temperature of the protein is reached. For example, insulin is sensitive to heat, and recent studies show that insulin should be aerosolized through a jet nebulizer (such as Aerx™ device [Aradigm Corporation, Hayward, California]) as opposed to a USN.³² Most currently available inhaled drugs are stable with use of a USN.³³ However, the breakdown of a drug can be a cumulative effect of surface denaturation, heat, cavitation, and direct pressure effects in a USN.³³ Drug solutions must be tested by using ultrasonic delivery to determine that activity is preserved, particularly when proteins or liposomes are nebulized. The clinician should refer to the manufacturer's directions to help determine which device should be used for each drug.

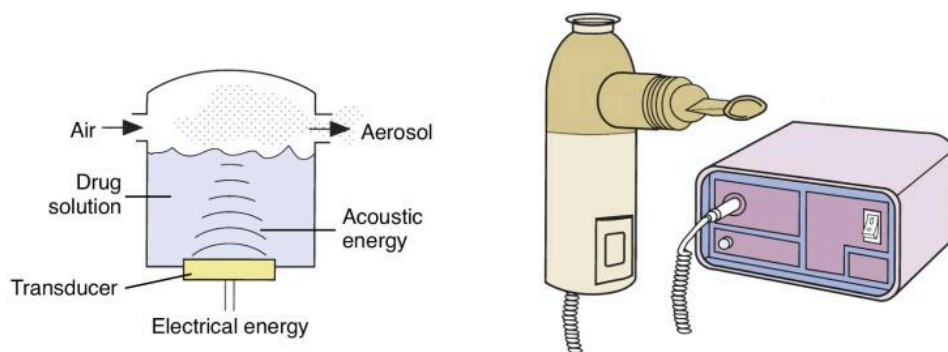
Factors Affecting Jet Nebulizer Performance. When using a jet nebulizer, it is important to control factors affecting jet nebulizer performance during aerosol drug administration. Various types of jet nebulizers are available on the market, and several



• **Fig. 3.11** Basic configurations of mesh nebulizer. **A**, Active vibrating mesh. **B**, Ultrasonic horn. **C**, Passive mesh. (**A**, Courtesy PARI Respiratory Equipment, Inc., Midlothian, Virginia. **B** and **C**, Courtesy Omron Healthcare Inc., Bannockburn, Illinois.)



• **Fig. 3.12** A, Aerosol is injected into the breath at the beginning of inspiration. Adaptive aerosol drug delivery through a passive mesh nebulizer, such as I-neb (B). (From Cairo, J. M. [2014]. *Mosby's Respiratory Care Equipment* [9th ed.]. St. Louis, Missouri: Elsevier; photo inset, courtesy Phillips Healthcare, Andover, Massachusetts.)



• **Fig. 3.13** Illustration of the principle of ultrasonic nebulization, with an example of a portable device used to aerosolize medications.

• BOX 3.3 Advantages and Disadvantages of Portable Ultrasonic Drug Nebulizers

Advantages

- Small size
- Rapid nebulization with shorter treatment times
- Smaller drug amounts with no diluent for filling volume
- Can be used during car travel or camping

Disadvantages

- High expense
- Fragility, lack of durability
- Requires electrical source (either AC or DC)
- Possible degrading effect on drug must be determined

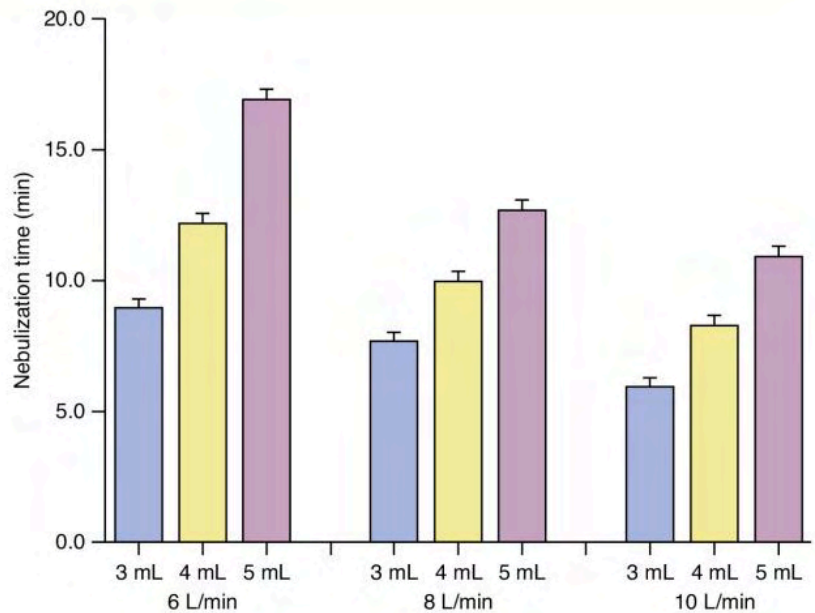
AC, Alternating current; DC, direct current.

studies have indicated that performance varies among products from different manufacturers and even among nebulizers from the same manufacturers.^{34–36} These factors include residual volume or “dead volume,” filling volume, treatment time, flow rate and pressure, output rate, continuous versus inspiratory nebulization, type of power gas, physical nature of the solution to be nebulized, humidity, temperature, and device interface. Some of these factors are reviewed in greater detail below.

Dead Volume (Residual Volume). Jet nebulizers do not aerosolize below a minimal volume, termed the **dead volume**, which is the amount of drug solution remaining in the reservoir when the device begins to sputter and aerosolization ceases. This volume can vary with the brand of nebulizer but is in the order of 0.5 to 1.0 mL. This is the primary reason why diluent, which is effectively additional volume, is added to 0.5 mL of a bronchodilator solution, such as albuterol. Adding diluent does not alter the amount of drug (dose) in the nebulizer; it simply “expands” the solution volume. The concentration of the solution is less, not the amount of drug (see Chapter 4 for further discussion). Drug loss with nebulization can also occur into the ambient air. As a result of these factors, the amount of dose available to be inhaled from a nebulizer is considerably less than the dose placed into the reservoir. Kradjan and Lakshminarayan³⁷ found that under clinical conditions of nebulization until sputter, approximately 35% to 60% of a drug solution was delivered from the nebulizer. Even with vigorous agitation, this amount increased to only 53% to 72%. A study by Shim and Williams³⁸ found that only 40% to 52% of the total dose was delivered from gas-powered nebulizers. In a positive-pressure circuit, this efficiency may decrease further, to approximately 30% of the total dose.³⁹ Evaporation of an aqueous solution not only causes cooling of the nebulizer and liquid but also can increase the concentration of solute in the residual (dead) volume.

Filling Volume and Treatment Time. Based on the work of Hess and associates,³⁵ Fig. 3.14 shows the relationship of volume

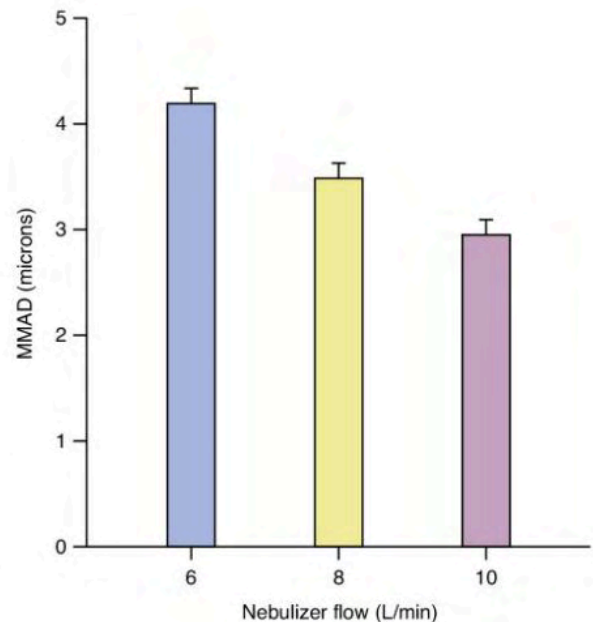
• **Fig. 3.14** Relationship of volume and flow rate to time of nebulization averaged for 17 gas-powered nebulizers. (From Hess, D., Fisher, D., Williams, P., et al. [1996]. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer band. *Chest*, 110, 498.)



and flow rate to the time of nebulization, presented as the pooled average performance of 17 nebulizer brands. Increasing the volume increases the time of effective nebulization at any given flow rate. At less than 2 mL, most pneumatic nebulizers do not perform well because the volume is close to the dead volume—that is, the residual amount that does not nebulize. At 6 mL, an excessively long time is required for treatment (>10 minutes) with most brands. Although 5 minutes seems to be a short time, even this can be inconveniently long as a way of taking medication three or four times a day; some patients have difficulty in taking a pill four times a day, an approximately 2- to 3-second activity. Patient compliance is directly proportional to convenience. Given the volume requirements of nebulizers for efficient operation and the need for relatively brief treatments, a volume between 3 and 5 mL of solution is recommended, unless the nebulizer is specifically designed for a smaller fill volume. Increasing the volume also decreases the concentration of a drug remaining in the dead volume when nebulization ceases.³⁵ The dose of a drug available to the patient is increased, although treatment times also increase at any given flow rate.

Increasing fill volume increases inhaled efficiency and the dose to the patient. It should be noted that the approved label dose of the drug includes the fill volume that was used in the clinical trials that lead to approval by the US Food and Drug Administration (FDA). Increasing fill volume would increase the dose to the patient and should not be done without consulting with the prescribing physician.

Effect of Flow Rate and Pressure. A second practical question concerns the flow rate at which to power jet nebulizers. The flow rate affects two variables: the length of treatment time and the size of the particles produced. Fig. 3.14 illustrates the interaction between volume and the flow rate in determining the time of nebulization. At a flow rate of 6 L/min, a volume of 3 mL requires less than 10 minutes; at 10 L/min, a volume of 5 mL can be nebulized in approximately 10 minutes. Fig. 3.15 shows the effect of flow rates on particle size of the aerosol produced, averaged for the 17 nebulizers studied by Hess et al.³⁵ With pneumatically powered nebulizers, increasing the flow rate decreases the particle size and shifts the MMAD lower. On the basis of the results of Hess et al.



• **Fig. 3.15** Effect of power gas flow rate on the mass median aerodynamic diameter (MMAD) of aerosol particles produced on average by 17 gas-powered nebulizers. (From Hess, D., Fisher, D., Williams, P., et al. [1996]. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer band. *Chest*, 110, 498.)

shown in Figs. 3.14 and 3.15, average optimal rates are a filling volume of 5 mL and a flow rate of 6 to 8 L/min for many nebulizers. Also, each model of jet nebulizer is designed to work best at a specific flow, ranging from 2 to 8 L/min. It is important to operate a jet nebulizer with a compressor or a gas flow that matches the intended design; at a lower flow or pressure, particle size would increase. If a jet nebulizer designed to operate at 6 to 8 L/min at 50 pounds per square inch (psi) is driven by a compressor producing 13 psi, it will produce a larger particle size, which will influence efficiency.²⁷

Type of Power Gas. Use of gases other than oxygen or air can change the performance characteristics of a nebulizer. Hess et al.³⁵ showed that the use of heliox (a mixture of helium and oxygen) to nebulize albuterol caused particle size and inhaled drug mass to decrease, along with a greater than twofold increase in nebulization time. Increasing the flow of heliox returned output to that seen with air.⁴⁰ The flow rate should be increased by 1.5 to 2 times during heliox-driven aerosol drug administration to bring particle size and output back to levels achieved with air or oxygen.^{27,41,42} Selection of the appropriate gas to power a nebulizer needs to be done by the practitioner on the basis of patient data or policy and procedure set by the institution. Oxygen has always been used because of its availability; however, using air to control the oxygen a patient receives may be of importance to practitioners.

Device Interface. Device interfaces used for aerosol drug administration include mouthpieces and face masks. Ideally, a mouthpiece should be used because studies suggest that the mouthpiece provides greater lung dose than a standard pediatric aerosol mask.^{43,44} Also, use of a face mask increases the amount of aerosol deposited on the face, in the eyes, and into the nose, which can be particularly significant for certain drugs, such as inhaled corticosteroids. A mouthpiece cannot be used by infants and children, and it is also uncomfortable for longer aerosol therapy. Regardless of the type of device interface used during aerosol therapy, patients should be instructed to inhale through the mouth because the nose tends to filter more aerosol compared with the mouth.²⁷

Type of Solution. Droplet size of nebulized solutions is related to surface tension and viscosity of the solution and is partially determined as well by the baffles in the device.⁴⁵ Recommended filling volumes and flow rates are suitable for the aqueous bronchodilator solutions usually administered with these devices. However, the volumes and flow rates suggested may require modification for some drug solutions, such as pentamidine or antibiotics, which have different physical characteristics and viscosities. For example, higher-viscosity antibiotic solutions of gentamicin or carbenicillin require power gas flow rates of 10 to 12 L/min to produce suitably small aerosol particles for inhalation with some jet nebulizers.⁴⁶ Some disposable nebulizers may exhibit greater variability in performance or not achieve adequate output characteristics with new or nonbronchodilator drug solutions. The performance of a jet nebulizer should be tested with various drug solutions, and newly introduced nebulizer drugs should be tested with an intended nebulizer system to ensure adequate performance. It is best to nebulize only drugs that have been manufactured for nebulization; however, it is common to nebulize agents intended for a different route of administration. Nebulizers not tested for performance with a new or unknown drug solution cannot be assumed to produce adequate output and particle sizes. As indicated in Chapter 2 in the review of lung availability/total systemic availability (L/T) ratios and the pharmacokinetics of inhaled aerosol drugs, efficiency of lung delivery is a function of *both* drug and device. The drug–device combination should be tested before clinical use.

Table 3.1 lists some tested and adequate drug–device combinations for nebulizer delivery. Additives to the drug solution can also affect aerosol characteristics and drug delivery.²⁷ See Box 3.4⁴⁷ for helpful information on the use and cleaning of jet nebulizers.

Pressurized Metered Dose Inhalers

The pMDI has been in use since its development by Maison in 1955.⁴⁸ These devices are most commonly aerosol generators

TABLE 3.1 Representative Drug–Device Combinations Tested for Nebulizer Drug Delivery

Drug	Approved Nebulizer
Bronchodilator	Nebulizer type not specified
Acetylcysteine	Nebulizer type not specified
Budesonide (Pulmicort Respules)	Should not be used with ultrasonic nebulizer
Tobramycin (Bethkis, TOBI)	Pari LC
Aztreonam (Cayston)	Altera Nebulizer System
Dornase alfa (Pulmozyme)	Hudson T Up-draft II, Marquest Acorn II, Pari LC, Durable Sidestream, Pari Baby
Pentamidine (NebuPent)	Marquest Respirgard II
Ribavirin (Virazole)	Small particle aerosol generator (SPAG)
Iloprost (Ventavis)	ProDose or I-neb
Treprostinil (Tyvaso)	Tyvaso Nebulizer System
glycopyrrolate (LONHALA)	MAGNAIR

From Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.

prescribed for patients with asthma and chronic obstructive pulmonary disease (COPD); they are small, pressurized canisters for oral or nasal inhalation of aerosol drugs and contain multiple doses of accurately metered drug. Advantages and disadvantages of drug delivery by pMDI are listed in Box 3.5.

Technical Description

A pMDI has five major components:

1. Canister
2. Propellant/excipient mixture
3. Drug formulary
4. Metering valve
5. Actuator and dose counter

Fig. 3.16 illustrates the major components of a pMDI as well as the function of the metering valve. The characteristics of each pMDI component are described in Table 3.2.

The drug in a pMDI is either a suspension of micronized powder in a liquefied propellant or a solution of the active ingredient in a cosolvent (usually ethanol) mixed with the propellant. Dispersing agents, or *surfactants*, are added to prevent aggregation of drug particles and to lubricate the valve mechanism, thereby maintaining suitable particle sizes in the aerosol plume, aerosol particles discharged from a pMDI, produced in CFC (e.g., Freon) devices. These surfactants are not soluble in HFA devices.⁴⁹ In his report, Newman⁵⁰ presented a detailed technical description of the complexities involved in producing a pMDI.

Chlorofluorocarbon Versus Hydrofluoroalkane Propellants

Historically, CFCs and HFAs were the two types of propellants used with pMDIs. In the past, blends of liquefied gas (CFCs) were used with pMDIs to create an aerosol, but because one CFC

• BOX 3.4 Use of Small Volume Nebulizers

Generic Recommendations That Apply to All Nebulizers²⁷

1. Read and follow instructions before using nebulizer.
2. Ensure that nebulizer is properly assembled, according to the manufacturer's instructions.
3. Ensure that nebulizer is cleaned and dried between treatments.
4. Ensure that nebulizer is operated in its proper orientation.

Critical Steps in Jet Nebulizer Use²⁷

5. Assemble all parts of nebulizer before treatment including tubing, nebulizer cup, and mouthpiece or mask.
6. Put drug into nebulizer cup.
7. Sit in the upright position.
8. Connect nebulizer to power source, such as compressed air, oxygen, or a compressor.
9. Breathe normally during treatment, taking occasional deep breaths until sputter occurs or until end of nebulization.
10. Keep nebulizer in vertical position during treatment.
11. Rinse nebulizer with sterile or distilled water.
12. Allow to air dry.

Critical Steps in Vibrating Mesh and Ultrasonic Nebulizer Use²⁷

13. Correctly assemble nebulizer according to the manufacturer's instructions.
14. Follow the manufacturer's instructions in performing functionality test before first use of the new nebulizer and after each disinfection to verify proper operation.
15. Place medicine into medication reservoir. Do not exceed volume recommended by manufacturer.
16. Sit in upright position.
17. Turn on power.
18. Hold nebulizer in position recommended by the manufacturer.
19. Breathe normally during treatment, taking occasional deep breaths.
20. Turn off unit to avoid waste if treatment must be interrupted.
21. Disassemble and clean the nebulizer after treatment, as recommended by the manufacturer.
22. When using VMN, do not touch vibrating mesh during cleaning because it will damage unit.
23. Disinfect nebulizer, according to the manufacturer's instructions, once or twice a week.

Common Errors in Use²⁷

- Failure to assemble nebulizer properly
- Wasting dose by tilting (some nebulizers)
- Failure to keep mouthpiece in mouth during treatment
- Failure to mouth breathe during nebulization

Cleaning Instructions for Small Volume Nebulizers²⁷

VMNs and USNs should be cleaned and disinfected according to the manufacturer's instructions. During the cleaning of VMNs, the mesh should not

USN, Ultrasonic nebulizer; VMN, vibrating mesh nebulizer.

From Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.

be touched to prevent damage to the unit. For jet nebulizers, the Cystic Fibrosis Foundation guidelines⁴⁷ recommend washing the parts of jet nebulizers with soap and hot water after each treatment, taking care to avoid damaging any parts of the aerosol generator. Also, nebulizers should be cleaned after every treatment at home. The longer a dirty nebulizer sits and is allowed to dry, the harder it will be to clean thoroughly. Rinsing and washing the nebulizer immediately after each treatment reduces the risk of infection. Cleaning instructions for the jet nebulizer are as follows:

Cleaning Instructions for the Jet Nebulizer²⁷

Cleaning After Each Use

- Wash hands before handling equipment.
- Disassemble parts after every treatment.
- Remove tubing from compressor and set aside; tubing should not be washed or rinsed.
- Rinse nebulizer cup and mouthpiece with either sterile water or distilled water.
- Shake off excess water.
- Air dry on absorbent towel.
- Store nebulizer cup in resealable plastic bag.

Cleaning Once or Twice a Week

- Wash hands before handling equipment.
- Disassemble parts after every treatment.
- Remove tubing from compressor and set aside; tubing should not be washed or rinsed.
- Wash nebulizer parts in warm water with liquid dish soap.
- Disinfect nebulizer, according to manufacturer's instructions; nebulizer parts may be soaked in one of the following solutions:
 1. 1 part household bleach in 50 parts water for 3 minutes
 2. 70% isopropyl alcohol for 5 minutes
 3. 3% hydrogen peroxide for 30 minutes
 4. 1 part distilled white vinegar in 3 parts hot water for 1 hour (not recommended for patients with cystic fibrosis)
- Rinse parts with sterile or distilled water.
- Shake off excess water and place all parts on clean paper towel.
- Allow parts to air dry completely on absorbent towel.
- Reassemble nebulizer and store in clean dry bag or container.

molecule can destroy 100,000 molecules of stratospheric ozone, the FDA banned the use of CFC-pMDIs. The few remaining CFC aerosol devices were removed from market on December 31, 2013. Hydrofluorocarbons (HFCs), or *HFAs*, were then identified as propellants that were nontoxic to the atmosphere and to the patient and that also had properties suitable for MDI aerosol generation. In particular, HFA 134a has a vapor pressure similar to that of CFC 12. The structure of HFA 134a is illustrated in Fig. 3.17 and compared with that of CFC 12. Replacement of

CFC propellants has led to overall reengineering of pMDI components (valve, seals, exit orifice, and drug formulation), which has improved pMDI performance. Some of the differences, such as the lower plume force (Fig. 3.18) and warmer plume temperature, cause patients who have used CFC-propelled pMDI formulations to think there is reduced or no drug delivery occurring with the HFA formulation of albuterol.⁵¹

Equivalence and Safety. The efficacy and safety of all reformulated HFA drugs have been studied. It should be noted that

• BOX 3.5 Advantages and Disadvantages of Pressurized Metered Dose Inhalers

Advantages

- Pressurized metered dose inhalers (pMDIs) are portable, light, and compact.
- Drug delivery is efficient.
- Treatment time is short.
- They are easy to use.
- More than 100 doses are available.
- Fine particle sizes are available in hydrofluoroalkane (HFA) formulations.
- pMDIs are difficult to contaminate.
- No drug preparation is needed.
- It is possible to reproduce emitted doses.

Disadvantages

- Complex hand-breathing coordination, proper inhalation pattern, and breath hold are required.
- Drug concentrations and doses are fixed.
- Canister depletion is difficult to determine accurately.
- Reactions to the propellants may occur in small percentage of patients.
- High oropharyngeal impaction and loss occur if an extension device is not used.
- Foreign body aspiration of coins and debris from mouthpiece can occur*.
- Difficult to determine dose remaining in canister without dose counter.

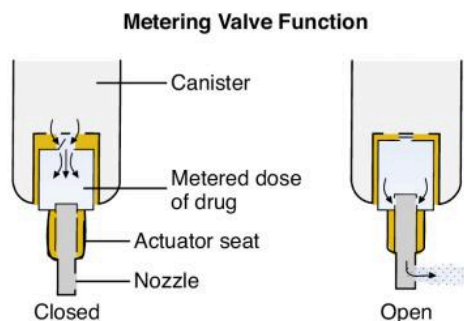
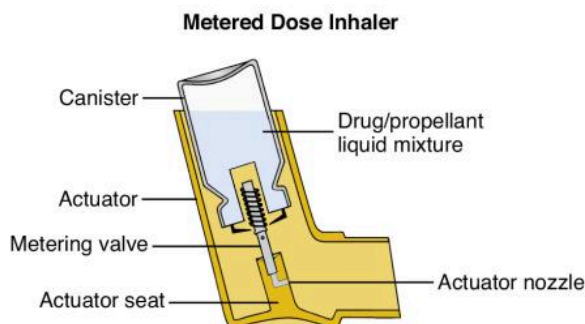
*Data from Hannan, S. E., Pratt, D. S., Hannan, J. M., & Brienza, L. T. (1984). Foreign body aspiration associated with the use of an aerosol inhaler. *American Journal of Respiratory Disease*, 129, 1205; Schultz, C. H., Hargarten, S. W., & Babbitt, J. (1991). Inhalation of a coin and a capsule from a metered-dose inhaler [letter]. *New England Journal of Medicine*, 325, 432.

TABLE 3.2 Basic Components of Pressurized Metered Dose Inhaler

Component	Particulars
Canister	Inert, able to withstand high internal pressures and use a coating to prevent drug adherence
Propellants	Liquefied compressed gases in which drug is dissolved or suspended
Drug formulary	Particulate suspensions or solutions in presence of surfactant or alcohol that allocates drug dose and specific particle size
Metering valve	Most critical component; crimped onto container and is responsible for metering a reproducible volume or dose; elastomeric valves are responsible for sealing and prevention of drug loss or leakage
Actuator	Frequently referred to as “boot”; partially responsible for particle size based on length and diameter of nozzle of various pMDIs; each boot is unique to a specific pMDI/drug
Dose counter	Provides visual tracking of number of doses remaining in pMDI

pMDI, Pressurized metered dose inhaler.

From Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.



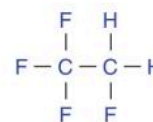
• **Fig. 3.16** Major components of a metered dose inhaler, with an illustration of the function of the metering valve. Oral and nasal adapters are shown.

Propellant 12
(chlorofluorocarbon)



Density: 1.22 g/mL
Boiling point: -29.8°C
Vapor pressure (psig at 20°C) 67.6 psig

Propellant 134a
(hydrofluoroalkane)

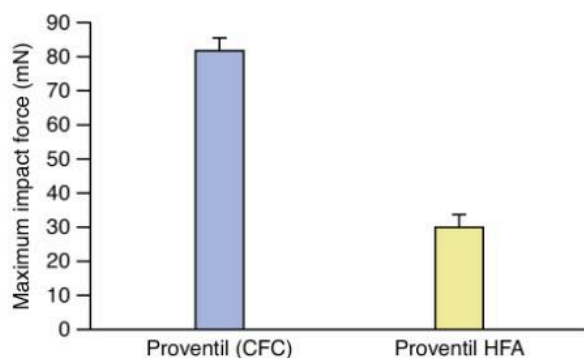


Density: 1.21 g/mL
Boiling point: -26.5°C
Vapor pressure (psig at 20°C) 68.4 psig

• **Fig. 3.17** Structure and properties of a chlorofluorocarbon (CFC) propellant, CFC 12, and a non-CFC propellant, hydrofluoroalkane 134a, used in pressurized metered dose inhaler drug formulations.

the amount of drug may have changed from the CFC form, but many companies have reformulated products to maintain similar strength and dose.

Improved Drug Delivery With Hydrofluoroalkane Formulation. Although equivalent drug amounts and effects were found with the drugs, the reengineering of the MDI for HFA propellant has resulted in significant improvements in performance, in particular, in lung deposition of the aerosol drug. The traditional amount of 10% for lung deposition has been increased more than fivefold with some HFA formulations.⁵² Fig. 3.19 illustrates a comparison of lung delivery between HFA-based and CFC-based MDI systems and the increase in lung delivery when the HFA formulation is used.



• **Fig. 3.18** Measures of plume force exiting a metered dose inhaler for chlorofluorocarbon (CFC)-propelled and hydrofluoroalkane-propelled albuterol (Proventil and Proventil HFA). (Data from Ross, D. L. & Gabrio, B. J. [1999]. Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system, *Journal of Aerosol Medicine*, 12, 151.)

CLINICAL CONNECTION

Metered dose inhalers are an excellent choice for drug delivery for the right patient. Many limitations exist, but most can be overcome by using a spacer or valved-holding chamber.

Types of Pressurized Metered Dose Inhalers

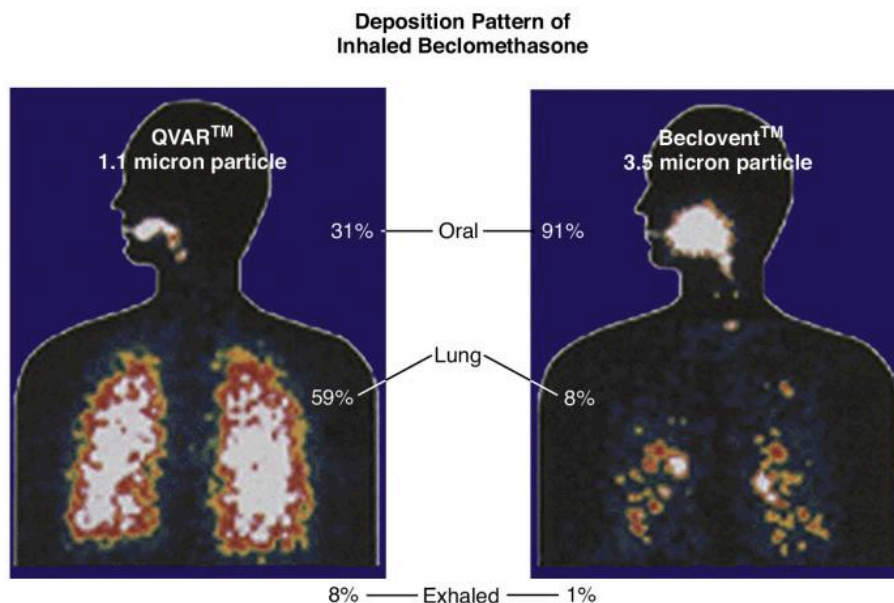
pMDIs can be divided into three categories: (1) conventional pMDIs, (2) breath-actuated pMDIs, and (3) a soft mist inhaler.

Conventional Pressurized Metered Dose Inhaler. The conventional pMDI has a press-and-breathe design. Fig. 3.16 illustrates the components of the conventional pMDI, including the canister, medication, propellant/excipient, metering valve, mouthpiece, and actuator. When the canister is depressed into the actuator, the drug-propellant mixture in the metering valve is

released under pressure. The liquid propellant rapidly expands and vaporizes, or “flashes,” as it ejects from the pressurized valve into ambient pressure. This expansion and vaporization shatter the liquid stream into an aerosol. The initial vaporization of propellant causes cooling of the liquid-gas aerosol suspension, which can be felt if discharged onto the skin; however, HFA versions have a much “warmer” spray temperature. The cold mist from a CFC spray may cause users to stop inhaling as the cold aerosol hits the oropharynx. On release, the metering valve refills with the mixture of drug and propellant from the bulk of the canister and is ready for the next discharge. The metering valve varies from 25 to 100 μL in volume⁵⁰ and provides 50 mcg to 5 mg of drug per actuation, depending on the drug formulary.²⁷

Breath-Actuated Pressurized Metered Dose Inhaler. A type of device to simplify MDI use is a breath-actuated adapter. In the United States, the adrenergic bronchodilator pirbuterol (Maxair, Valent Pharmaceuticals, Montreal, Quebec, Canada) (see Chapter 6) was marketed as a breath-actuated inhaler. Maxair was removed from the market for containing CFC propellant. It is not known if the device will be returned to the market with an HFA propellant. Breath-actuated inhalers offer an alternative for individuals who find it difficult to coordinate pMDI actuation with inhalation. As described by Newman,⁵⁰ Newman et al.,⁵³ and Baum and Bryant,⁵⁴ the pMDI canister is triggered by a spring through a triggering mechanism activated when the patient inhales. Evidence indicates that breath-actuated pMDIs improve the delivery of inhaled medication in patients with poor coordination.⁵⁵ However, if the patient has good coordination with the conventional pMDI, the use of a breath-actuated pMDI may not improve drug delivery.^{53,55}

Respimat Soft Mist Inhaler. The Respimat (Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut) is a propellant-free soft mist inhaler utilizing mechanical energy in the form of a tension spring. Turning the transparent base one-half turn to the right draws a predetermined volume of solution from the medication cartridge through a capillary tube into the micropump.



• **Fig. 3.19** Comparison of lung deposition between chlorofluorocarbon (right) and hydrofluoroalkane (left) formulations of beclomethasone dipropionate by metered dose inhaler (MDI). (Scintigraph and data courtesy C. Leach, Lovelace Respiratory Research Institute, Albuquerque, New Mexico.)



• **Fig. 3.20** Picture of Respimat Soft Mist inhaler. (Courtesy Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut.)

Depressing the dose release button releases energy from the spring, forcing solution to the mouthpiece and producing a soft mist of aerosol lasting 1.5 seconds.²⁷

The Respimat needs to be primed before use and if it has not been used for 21 days or more. It is recommended to actuate the inhaler once if it has not been used for 3 days. Any actuations or repriming after the initial priming will result in loss of medication actuations. The Respimat (Fig. 3.20) does not need to be shaken, as it is propellant free. The device is equipped with a dose indicator and will lock itself after the last dose is used.

Breath-Actuated Pressurized Metered Dose Inhaler Accessory Devices. Numerous breath-actuated pMDI devices are available on the market. The MD Turbo (Respirics, Raleigh, North Carolina) and the SmartMist (Aradigm) are used with most pMDIs because they are able to convert a conventional pMDI to a breath-actuated pMDI through breath-triggering mechanisms.²⁷

Factors Affecting Metered Dose Inhaler Performance

The accuracy and consistency of dose from pMDIs may be more sensitive to handling practices than previously thought. Research on the drug content of albuterol sprays by pMDI has shown that various factors affect dose consistency.

Loss of Dose. *Loss of dose* refers to the loss of drug content in the valve even though propellant may seem to discharge a normal dose. A dose with less than the nominal amount of drug has been noted to occur when first actuating an albuterol MDI that has been stored in the valve-down position, even after only a few hours and with shaking before discharge. The loss of dose ranged from 25% to greater than 50% in the studies referenced.^{56,57} This loss of dose was not observed with storage in a valve-up position. Other drug formulations may increase or decrease drug concentration in the first discharge after standing unused; this would need to be determined for each product. These findings suggest that the canister be stored valve up between uses and that a waste dose be discharged if greater than 4 hours have elapsed with the valve down when using albuterol via pMDI. The new HFA formulation is not associated with loss of dose.¹⁴

Shaking the Canister. Many of the drugs in MDI formulations are suspensions that can separate from the propellants on standing (*creaming*).⁵⁷ This separation should not affect the dose

in the valve, filled after the previous actuation. However, if the suspended drug is either lighter or heavier than the propellant and separation occurs, a second actuation could deliver more or less concentrated drug if the canister is not shaken to mix the propellant and drug suspension thoroughly. The MDI should be shaken *before* the first actuation after standing so that the metering valve refills with adequately mixed suspension from the canister. Everard et al.⁵⁷ found that not shaking an albuterol canister before use and after the canister has been standing upright overnight led to a 26% reduction in total dose and a 36% reduction in particles less than 6.8 μm ; this occurred despite wasting two discharges before the measurement. Rubin and Durotoye⁵⁸ found similar results with CFC inhalers, but HFA beclomethasone did not seem to be influenced by shaking of the canister.

Timing of Actuation Intervals. A pause of 1 to 5 minutes has been advocated between each puff of a bronchodilator from an MDI in an attempt to improve distribution of the inhaled drug in the lung.⁵⁹ The study by Everard et al.⁵⁷ found that two actuations of albuterol MDI 1 second apart caused no change in total drug output, although there was a 15.8% decrease in the amount of particles less than 6.8 μm . However, four actuations 1 second apart led to significant reductions in dose output. Concern over cooling of the MDI valve with rapid actuations does not seem to be supported by the results presented by Everard et al.⁵⁷ Loss of dose probably occurs as a result of turbulence and coalescence of particles with more than two rapid actuations. Clinically, a pause between puffs from an MDI has not been found to be beneficial in routine maintenance therapy. Pedersen⁶⁰ showed no difference in forced expiratory volume in 1 second (FEV_1) with a 3-minute and 10-minute divided dose under nonacute basic maintenance conditions. This was found to be the case for a β agonist (terbutaline) and a corticosteroid (budesonide) when used by preadolescents.⁶¹ However, during asthma exacerbations with acute wheezing, a pause between puffs resulted in significantly improved bronchodilation, with greater effect with use of a 10-minute pause.⁵⁹

There is no consensus on any of the preceding information covered. It is best to educate the health care practitioner and the patient about applying a systematic approach when using an MDI. The better the routine and consistency in using this device, the more likely it is that patients will benefit.

Loss of Prime. *Loss of prime* refers to the loss of propellant from the metering valve of the MDI.⁶² When this occurs, little or no drug is discharged on actuation; this can be felt and heard by a user. Loss of prime usually takes days or weeks to occur; regular use of the MDI should prevent this. Shaking of the canister and discharge of a waste dose are suggested after long periods of no use to prime the valve with propellant and drug.

Storage Temperature. Data indicate that dose delivery from CFC-propelled MDIs of albuterol decreases at lower temperatures. A significant decrease of 65% to 70% of the usual dose has been observed at 10°C. An even greater decrease was observed in a fine particle mass (<4.7 μm), with approximately 75% of the usual dose at 10°C and only 25% at -10°C. No medication was delivered at -20°C.⁶³ In contrast, HFA-propelled albuterol remained constant in total dose over the range of -20°C to 20°C. The fine particle mass of the CFC-free formulation decreased significantly only at -20°C, delivering approximately 60% of the initial FPD. Such temperature effects are likely to be relevant only for outdoor use of MDI canisters in extreme weather.

Nozzle Size and Cleanliness. Aerosol drug delivery with a pMDI is dependent on nozzle size, cleanliness, and lack of moisture.²⁷ The size of nozzle is specific to the pMDI and influences

not only the inhaled dose but also the particle size. The inverse relationship between the inner diameter and the nozzle extension and the amount of drug delivered to the patient has been documented.⁶⁴ According to Niven et al.,⁶⁴ a nozzle extension with an inner diameter less than 1 mm increases aerosol drug delivery. Because white and crusty residue resulting from crystallization of medication may influence drug delivery, the nozzle should be checked and cleaned periodically according to the manufacturer's recommendations.²⁷

Breathing Technique. The two primary techniques for using a pMDI without a spacer are the *open mouth* technique and the *closed mouth* technique. Actuating the pMDI several centimeters in front of the open mouth theoretically allows for slowing of the particle velocity and evaporation of aerosol droplets, resulting in less oropharyngeal impaction and loss. This maneuver further complicates the use of the pMDI. The manufacturers of pMDIs universally recommend the closed mouth technique for effective use of a pMDI. Although some studies with both children and adults have shown no difference in lung function between an open mouth and a closed mouth technique in use of a bronchodilator,^{65,66} others recommend the open mouth technique in an attempt to reduce oropharyngeal deposition and increase lung dose.^{67,68} Consequently, the simpler technique should be preferred. If oropharyngeal impaction is undesirable, as in the case of inhaled corticosteroids, or if accurate timing between actuations is a problem, as is sometimes the case for older patients, an extension device (spacer or holding chamber) should be used. More drug—equivalent to the output of a standard SVN—is inhaled from the pMDI with the use of an extension device.⁶⁹

Patient Characteristics. Characteristics of the patient using the pMDI lead to a variability of aerosol deposition. For instance, aerosol deposition is lower in infants and children because of differences in their anatomy and physical and cognitive abilities.^{27,70}

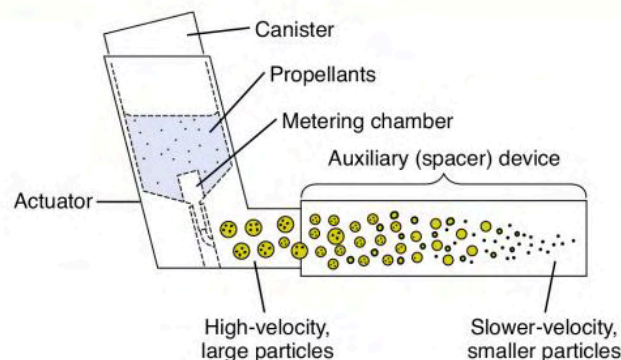
Correct Use of a Pressurized Metered Dose Inhaler

The effectiveness of treatment with an aerosolized drug delivered by a pMDI depends on correct use of the device. The major problem with pMDI devices is difficulty in patient use.⁷¹ The most common error noted is the failure to coordinate inhalation and actuation of the inhaler (hand-breathing incoordination). Other problems include a too-rapid inspiratory flow rate, inadequate or missing breath hold after inhalation, failure to shake and mix canister contents, cessation of inspiration as the aerosol strikes the throat, actuation of the pMDI at total lung capacity, inhaling through the nose, and exhaling during actuation. Evidence indicates that 50% to 70% of patients do not use pMDIs correctly.⁶⁹ In addition, physician, nurse, and respiratory therapist (RT) knowledge of correct pMDI use is often inadequate for patient education⁶⁹ (Box 3.6).

Accessory Devices for Pressurized Metered Dose Inhalers

Extension, or reservoir, devices were introduced primarily to simplify the complex coordination of aiming, actuating, and breathing with a pMDI. Fig. 3.21 illustrates a generic reservoir device. Using accessory devices with pMDIs improves the effectiveness of aerosol drug administration because pMDI accessory devices can modify the aerosol discharged from a pMDI in the following three ways:

1. Such devices allow space and time for more vaporization of the propellants and evaporation of initially large particles to smaller sizes.



• **Fig. 3.21** The effect of an extension device on aerosol particle size and velocity from a metered dose inhaler.

2. Reservoirs allow the high initial velocity of particles released from a pMDI to slow before reaching the oropharynx. Particles discharged from the actuator nozzle have velocities exceeding 30 m/sec. By holding the actuator 4 cm in front of the mouth or by using an extension device, this velocity is allowed to slow.⁶⁷
3. As holding chambers for the aerosol cloud release, reservoir devices separate the action of actuation of the canister from inhalation and simplify the coordination required for effective use.

The combined effect of the first two advantages reduces oropharyngeal deposition. This reduces the amount of drug swallowed and absorbed from the gastrointestinal tract and reduces any local oropharyngeal side effects, such as those seen with inhaled corticosteroids. Box 3.7 summarizes the advantages and disadvantages of accessory devices.

Types of Pressurized Metered Dose Inhaler Accessory Devices. Many types of pMDI accessory devices are available on the market. The size ranges from 70 to 80 mL to 750 mL for some European brands; some are available with a mask. Numerous terms are used to refer to such devices, including *spacer*, *reservoir*, *auxiliary device*, *extension device*, *holding chamber*, and *add-on device*. Some distinction of terms may be useful to denote significant design differences among these devices. The following terminology is offered, partially based on Dolovich⁷²:

Reservoir device: Global term describing or referring to extension, auxiliary, and add-on devices attached to MDIs for administration. This term could include both “spacer” and “holding chamber.”

Spacer: Denotes a simple tube or extension device, with no one-way valves to contain the aerosol cloud; its purpose is simply to extend the MDI spray away from the mouth.

Valved holding chamber: Denotes a spacer device with the addition of a one-way valve to contain and hold the aerosol cloud until inspiration occurs.

Design Variables. Spacers are simple devices that extend the distance and space between the pMDI and the patient. pMDIs with spacers provide more drug to the patient compared with pMDIs without spacers. However, valved holding chambers can increase drug delivery, decrease oropharyngeal deposition, and help with coordination. Valves in the holding chamber act as a baffle reducing particle size, which reduces oropharyngeal impaction, and allow the patient to exhale without disrupting the aerosol inside the chamber. Valved holding chambers are superior to spacers.

• BOX 3.6 Use of Metered Dose Inhalers²⁷

The following instructions for the use of bronchodilator or corticosteroid aerosols with pMDIs are written in terms that may be helpful for patient education. Package inserts on particular agents should always be checked, and these protocols should be modified as needed, especially for other drug classes.

Generic Recommendations That Apply to All pMDIs²⁷

1. Remove mouthpiece cover of pMDI from boot.
2. Prime pMDI as directed in package insert.
3. Clean and dry boot of pMDI, according to the manufacturer's guidelines.
4. Track remaining doses after each use.

Critical Steps in Use of the Open Mouth Technique With pMDIs⁵

1. Remove cap, inspect for foreign matter, and push canister into nozzle receptacle of mouthpiece actuator.
2. Hold MDI in vertical position, shake inhaler, and, if not used recently, discharge priming dose.
3. Exhale to functional residual capacity (easier for subject) or to residual volume.
4. Hold MDI about 1 inch in front of open mouth or, alternatively, place in mouth with teeth apart and with tongue flat.
5. Begin to breathe in slowly through mouth while actuating inhaler by pressing down on canister. Inspiration should take about 3 to 4 seconds.
6. Continue inhaling to total lung capacity and hold breath for up to 10 seconds (only one puff for inhalation).
7. Exhale normally, shake canister, wait 20 to 30 seconds to allow valve to refill, and repeat dose, if prescribed.
8. Keep a diary of number of uses or use a counting device to keep track of number of actuations used.

Note: If you have trouble aiming the MDI at your open mouth, you can place the mouthpiece directly in your mouth and rest it on the lower front teeth without sealing your lips around it. If you find it hard to coordinate breathing and activating the MDI, you may wish to ask your physician to prescribe a reservoir device.

Critical Steps in Use of the Closed Mouth Technique With pMDIs²⁷

1. Remove mouthpiece cover and check for foreign objects.
2. Shake inhaler thoroughly.
3. Prime pMDI into air if it is new or has not been used for several days.
4. Sit up straight or stand up.
5. Exhale all the way out.
6. Place pMDI between teeth.
7. Ensure that tongue does not block pMDI by keeping it flat under mouthpiece.
8. Seal lips.
9. Actuate pMDI as you begin to inhale slowly.
10. Hold breath for 10 seconds or as long as possible.
11. Wait 1 minute before administering another puff of medicine.
12. Repeat steps 2 through 10 until dosage prescribed by physician is reached.
13. After using a corticosteroid, rinse mouth after last puff of medicine.
14. Spit water out and do not swallow any.
15. Replace mouthpiece cover on pMDI after each use.

Critical Steps in Soft Mist Inhaler (Respimat) Use

1. Close mouthpiece cap; press safety catch while pulling off clear base.
2. On label of inhaler, write discard date, which is 3 months from date cartridge is inserted into device.
3. Remove medication cartridge from box.
4. Push narrow end of cartridge into inhaler.
5. Return clear base to mouthpiece assembly.
6. Hold inhaler upright, with cap closed, to avoid accidental release of dose.
7. Turn clear base one-half turn.
8. Point inhaler toward ground and press dose release button.
9. Continue steps 6 through 8 until mist of medication is seen.
10. Once mist is visible, repeat steps 6 through 8 three times.

11. Once primed, turn clear base one-half turn and open mouthpiece cap.
12. Breathe out, slowly emptying lungs; close lips around mouthpiece without covering air vents.
13. Point inhaler to back of throat, keeping inhaler parallel to ground.
14. While inhaling slowly and deeply, press dose release button; continue to breathe in slowly for as long as possible.
15. Hold breath for 10 seconds or as long as possible.
16. Repeat steps 12 through 15 until prescribed dose has been completed.
17. When complete, replace mouthpiece cover on inhaler.

To Inhale a Corticosteroid

Use the same procedure as described in the use of the open or closed mouth technique with these exceptions:

1. If using a bronchodilator and a corticosteroid, inhale bronchodilator first, and wait 1 to 2 minutes before inhaling corticosteroid.
2. Always use extension or spacer device when inhaling corticosteroid. If you do not have such a device, try to hyperextend (straighten) your head and neck as much as possible when inhaling (in other words, look at the ceiling).
3. Rinse your mouth and throat with water after finishing.

Common Errors in Use

The number of patients using pMDIs incorrectly ranges from 12% to 89%, according to available studies.⁶

- Failure to coordinate actuation with inhalation (27%)
- Too short a period of breath hold after inhalation (26%)
- Too rapid an inspiratory flow rate (19%)
- Inadequate shaking and mixing of contents before use (13%)
- Abrupt cessation of inspiration as aerosol strikes throat (6%)
- Actuation at total lung capacity (4%)
- Firing actuation into mouth but inhaling through nose (2%)
- Exhaling during actuation
- Placing wrong end of inhaler in mouth, or holding in wrong (nonvertical) position
- Failure to take cap off before use
- Firing of MDI multiple times during a single inhalation
- Covering air vents on specific inhalers (i.e., Respimat)

Cleaning Instructions for pMDIs²⁷ and Respimat

Cleaning pMDI

Frequency of cleaning: Clean once a week and as needed.
Look at hole where drug sprays out from inhaler.
Clean inhaler if you see powder in or around hole.
Remove pMDI canister from plastic container so that it does not get wet.
Rinse plastic container with warm water and shake out to remove excess water.
Dry overnight.
Replace canister inside mouthpiece and recap mouthpiece.

Cleaning Respimat

Frequency of cleaning: Clean once a week and as needed.
Remove mouthpiece cover.
Wipe outside of mouthpiece with damp cloth.
Wipe metal piece inside mouthpiece with damp cloth.
Clean outside of inhaler with damp cloth when needed.
Recap mouthpiece.
Store in cool, dry place.

Check Canister Fullness

The best approach is to keep a patient log of use, showing date of initial use and subsequent numbers of actuations each day. If a pMDI is used regularly (e.g., two actuations four times daily), the projected date of depletion can be calculated. For occasional use, tallies at the end of the day on a self-stick note kept in a convenient place, such as the bathroom, can be useful. Counting devices can be purchased that count the number of actuations during use. Some manufacturers have a built-in counter on the actuator (e.g., ProAir, Ventolin, and Flovent). Canister flotation in water is no longer recommended; it is imprecise, varies with different drugs, and can clog the pMDI nozzles.

• BOX 3.7 Advantages and Disadvantages of Pressurized Metered Dose Inhaler Accessory Devices

Advantages

- Reduced oropharyngeal drug loss
- Separation of pMDI actuation and inhalation steps
- Allows use of MDI during acute airflow obstruction with dyspnea
- Available with mask for children
- No drug preparation required
- Increased inhaled dose by twofold or fourfold compared with pMDI alone

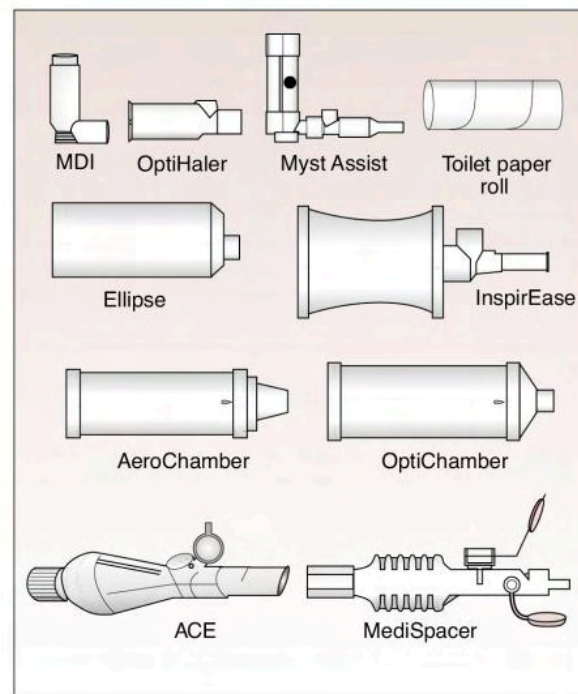
Disadvantages

- Large and cumbersome (some brands)
- Additional expense compared with pMDI alone
- Some assembly required
- Possible source of bacterial contamination with inadequate cleaning
- Patient errors in use of pMDI accessory devices such as firing multiple puffs into chamber before inhaling or a delay between actuation and inhalation

MDI, Metered dose inhaler; pMDI, pressurized metered dose inhaler. Modified from Gardenhire, D. S., Ari, A., Hess, D. R., & Myers, T. R. (2013). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (3rd ed.). Dallas, Texas: American Association for Respiratory Care.

pMDI accessory devices have several design variables, including volume, shape, direction of pMDI spray, presence of one-way valves, inspiratory flow rate indicators, and presence or absence of an integral (built-in) pMDI actuator. Table 3.3 summarizes these design variables for some reservoir devices available in the United States. Fig. 3.22 illustrates differences in the size and design of several units.

Electrostatic Charge. An electrostatic charge is inherent on most plastic holding chambers. It has been discovered that by reducing the electrostatic charge, an increase in drug delivery occurs. Simply washing the chamber with water and standard household detergent reduces the electrostatic charge, and the effects can last 30 days. Manufacturers have begun making chambers that are “antistatic.” Louca et al.⁷³ found that the AeroChamber MAX (Monaghan Medical Corp., Plattsburg, New York), a valved holding chamber made from antistatic plastic, performed better than other chambers that were washed and rinsed to reduce the electrostatic charge. Reducing electrostatic charge can increase delivery of the aerosolized drug by 70%.⁷⁴



• **Fig. 3.22** Pressurized metered dose inhaler (pMDI) and accessory devices consisting of spacer and holding chambers. All of the accessory devices reduce oropharyngeal deposition. Small volume spacers (OptiHaler and Myst Assist) offer no additional advantage, but large volume spacers (toilet paper roll and Ellipse) improve inhaled aerosol with delay between actuation and inspiration. Only the bag (InspirEase) and valved holding chambers (AeroChamber, OptiChamber, ACE, and MediSpacer) protect the patient from blowing the dose away when the pMDI is actuated during expiration. (From Kacmarek, R. M., Stoller, J. K., Heuer, A. J. [2017]. *Egan's Fundamentals of Respiratory Care* [11th ed.]. St. Louis, Missouri: Mosby.)

CLINICAL CONNECTION

Reducing electrostatic charge in a reservoir device can significantly increase drug delivery.

Size. The size of a spacer or holding chamber can affect the amount of drug made available to the patient: the larger the spacer, the greater is the amount of drug available. Most spacers in the United States are less than 200 mL. Larger chambers (up to 750 mL) are available outside of the United States. There is a

TABLE 3.3 Characteristics of Selected Reservoir Devices Used in the United States, Exemplifying Design Variable Differences

Brand	Volume (Approximate) (mL)	Inspiratory Valve	Spray Direction*	Flow Indicator	Integral Actuator
AeroChamber Plus	198	One way	Forward	Yes	No
OptiChamber Advantage	218	One way	Forward	No	No
ACE	175	One way	Reverse	Yes	Yes
InspirEase	600	No	Reverse	Yes	Yes
OptiHaler	70	No	Reverse	No	Yes
MediSpacer	160	No	Reverse	Yes	Yes

*Relative to mouth.

†Accepts mouthpiece actuator of drug brand.

tradeoff with inconvenience because the larger and bulkier devices are less likely to be used or taken on travels.

Dose Counters. pMDIs look, taste, and feel as if they are working after their label shows that the number of puffs contained were delivered to the patient; this is referred to as the “tail-off effect” with pMDIs, which may last long after the pMDI is empty of its drug.^{25,62} It is very important to use dose counters with pMDIs that allow patients and clinicians to determine the number of actuations used and the time when a pMDI should be discarded.^{75–77} The FDA also requires new pMDIs to have integrated dose counters and recommends that all pMDIs have dose-counting devices indicating when the pMDI is approaching its last dose. The Ventolin HFA (GlaxoSmithKline, Philadelphia, Pennsylvania) and Flovent HFA (GlaxoSmithKline) have built-in dose counters; mechanical or electronic dose counters are available from third parties and can be attached to a range of pMDIs. Although acceptable performance by and patient satisfaction with pMDIs with dose counters have been confirmed,^{78–80} some dose counters may be pMDI specific and may not fit the spacer, which leads to no or partial drug being emitted and a miscount of remaining doses.^{81,82} Using a dose counter increases the cost of aerosol therapy and may limit acceptance by patients. In that case, the number of doses remaining in the pMDI should be determined manually. Patients who wish to use a manual method should read the label to determine the total number of doses available in the pMDI and subtract every actuation given from the number of actuations on the label until all have been used. Although manual dose counting is cost effective, it may be impractical and undependable, especially in use of reliever medications on the go.²⁷ Note that floating the canister in water to determine the amount of medication remaining in the canister is misleading and can reduce the ability of the pMDI to work properly^{77,83,84} and should not be used. For instructions on general use, see [Box 3.8](#).

CLINICAL CONNECTION

Dry powder inhalers are an excellent choice for drug delivery for the right patient. The biggest limitation is inspiratory flow rate. The needed inspiratory flow rate is different for each device.

Dry Powder Inhalers

A DPI is similar to a pMDI except that the drug is in powdered form. The main advantage is that the DPI is breath actuated—that is, hand-breathing coordination is not needed. The main disadvantage is that the DPI requires a high inspiratory flow rate from the patient to dispense the drug. The flow rate needed is usually 30 to 90 L/min. Children and patients with respiratory disease may be unable to generate the flow needed to use such a device. [Box 3.9](#) lists advantages and disadvantages of DPIs.

Types of Dry Powder Inhalers

DPIs can be divided into three categories based on the design of their dose containers^{27,85}: unit-dose DPIs, multiple unit-dose DPIs, and multiple-dose DPIs. All types of DPIs have similar components incorporated with the inhaler, including a drug holder, air inlet, agglomeration compartment, and mouthpiece. Types of DPIs are illustrated in [Fig. 3.23](#).

Unit-Dose Dry Powder Inhalers. Unit-dose, or single-dose, DPIs have individually wrapped capsules that contain a single

dose of medication and deliver powder medication from a punctured capsule. Using a single-dose DPI involves several steps. First, the user places each capsule into the drug holder. Second, the user primes the device by piercing the single-dose capsule and allowing entrance of air into the device for dispersion with inhalation. The Neohaler and TOBI Podhaler (Novartis Pharmaceuticals, East Hanover, New Jersey), and HandiHaler (Boehringer Ingelheim Pharmaceuticals Inc.) are examples of single-dose DPIs.²⁷

Multiple Unit-Dose Dry Powder Inhalers. Multiple unit-dose DPIs disperse individual doses that are premeasured into blisters; the blister is mechanically punctured when the cover is lifted. The Diskhaler (GlaxoSmithKline) is an example of the multiple unit-dose DPI that requires an inspiratory flow rate greater than 60 L/min to achieve an adequate drug deposition into the lungs.²⁷ Relenza (zanamivir) is the only Diskhaler currently marketed in the United States.

Multiple-Dose Dry Powder Inhalers. Multiple-dose DPIs measure the dose either from a powder reservoir or from blister strips prepared by the manufacturers. Twisthaler (Merck & Co Inc., Whitehouse Station, New Jersey), the Flexhaler (AstraZeneca, Wilmington, Delaware), and Pressair (Forest Pharmaceuticals, St. Louis, Missouri) have a powder reservoir or storage area, whereas the Advair Diskus (GlaxoSmithKline) contains 60 doses of dry powder medication individually wrapped in blisters. Anoro Ellipta, Breo Ellipta, and Incruse Ellipta (GlaxoSmithKline) contain two double-foil strips with 30 blisters of each medication. The medication's blister wrapping protects the drug from humidity and other environmental factors.²⁷

Factors Affecting Dry Powder Inhaler Performance and Drug Delivery

Intrinsic Resistance. Intrinsic resistance of the DPI determines how much inspiratory flow must be created in the device to release the correct amount of the drug. Each type of DPI has a different intrinsic resistance to airflow. For instance, HandiHaler has a higher resistance than Diskus and requires a greater inspiratory effort. The patient's inspiratory effort is important not only in lifting the powder from the drug reservoir, blister, or capsule but also in deaggregating the powder into finer particles.²⁷

Inspiratory Flow Rate. Dispersal of drug powder depends on the energy of the inspiratory flow. A moderate to high inspiratory flow is needed with DPIs to obtain an optimal dose. This requirement affects the use of these devices by young children, especially those aged less than 5 years, and by any patient with an acute wheezing episode associated with airflow reduction. Patients should be evaluated for the ability to generate a minimal inspiratory flow before prescription of a DPI. [Fig. 3.24](#) illustrates the effect of various inspiratory flows with three DPI devices.

Humidity. Other factors that can affect dose delivery from a DPI are humidity and moisture, which can cause powder clumping and reduce deaggregation and the fine particle mass in the dose. Because a reservoir chamber containing multiple doses for dispensing has less protection from ambient humidity than capsules and drug blisters, DPIs with a reservoir chamber, such as Twisthaler, Flexhaler, and Pressair, must be kept as dry as possible. In contrast, Diskus and Ellipta, in which each drug dose is protected inside a blister on a foil strip, showed no change in 8 weeks under such conditions. With any DPI, it is essential that patients not exhale into the device before inhaling; in

• BOX 3.8 Use of Pressurized Metered Dose Inhaler Accessory Devices

The design and use of reservoir devices vary. The following steps are generic and are intended to describe most reservoir devices for handheld use. Specific brand instructions should be reviewed before use or instruction of patients.

Generic Recommendations That Apply to All pMDI Accessory Devices

1. Use nonelectrostatic material or prewash nonconductive material reservoir device.
2. To maximize dose, inhale simultaneously or right after actuating MDI.
3. Use a single inhalation with each MDI actuation. Multiple MDI actuations followed by a single inhalation reduces the dose available.
4. Have small children or infants inhale through device for five or six breaths to maximize emptying of chamber.
5. Ensure proper fit of pMDI to spacer or VHC.
6. Remove cap from pMDI boot.
7. Clean and reassemble pMDI spacers and VHCs based on the manufacturer's instructions.

Critical Steps in Use of Spacer or Valved Holding Chamber With pMDIs²⁷

1. Warm pMDI canister to hand or body temperature.
2. Take off mouthpiece cover and shake inhaler thoroughly.
3. Prime pMDI into air if it is new or has not been used for more than 24 hours.
4. Assemble apparatus and check for foreign objects.
5. Keep canister in vertical position.
6. Sit up straight or stand up.
7. Exhale all the way out.
8. Follow subsequent instructions based on type of device interface that you use.

With Mouthpiece

- a. Place mouthpiece of spacer between teeth and seal lips.
- b. Ensure that tongue does not block pMDI by keeping it flat under mouthpiece.
- c. Actuate pMDI as soon as you begin to inhale.
- d. Make sure to breathe in slowly; if device produces a whistle, it means that inspiration is too rapid.
- e. Move mouthpiece away from mouth and hold breath for 10 seconds or as long as possible.

With Mask

- a. Hold mask completely over nose and mouth and ensure it fits firmly against child's face.
- b. Actuate pMDI as child begins to breathe in.

MDI, Metered dose inhaler; *pMDI*, pressurized metered dose inhaler; *VHC*, valved holding chamber.

- c. Inhale slowly; if device produces a whistle, it means that inspiration is too rapid.
- d. Hold mask in place while child takes six normal breaths, including inhalation and exhalation.
- e. Remove mask from child's face.

With Collapsing Bag

- a. Open bag to its full size; press pMDI canister immediately before inhalation.
- b. Inhale until bag is completely collapsed.
- c. Breathe in and out of the bag several times to inhale all medication in bag.
- d. Wait 15 to 30 seconds if another puff of medicine is needed.
- e. Repeat steps a through d until dosage prescribed by physician is reached.
- f. Rinse mouth after treatment if corticosteroid is used.
- g. Spit water out and do not swallow any.
- h. Replace mouthpiece cover on pMDI.

Common Errors in Use

- Incorrect assembly
- Incorrect (nonvertical) position of pMDI canister on reservoir
- Waiting too long to inhale after actuating pMDI
- Inhaling too rapidly (may reduce dose)
- Firing of multiple puffs into reservoir before inhaling
- Firing of puffs from two different pMDIs before inhaling
- Failure to take mouthpiece cap off before use

Cleaning Instructions for pMDI Chamber and Collapsible Bag Device²⁷

Cleaning Chamber Device

- Frequency of cleaning: clean every 2 weeks and as needed.
- Disassemble device for cleaning.
- Soak spacer parts in warm water with liquid detergent and gently shake both pieces back and forth.
- Shake out to remove excess water.
- Air dry spacer parts in vertical position overnight.
- Do not towel dry spacer because this would reduce dose delivery as a result of static charge.
- Replace back piece on spacer when it is completely dry.

Cleaning Collapsible Bag Device

- Frequency of cleaning: clean every 2 weeks and as needed.
- Disassemble device for cleaning.
- Remove plastic bag assembly from mouthpiece.
- Wash mouthpiece with warm water.
- Drip dry the device overnight.
- Reassemble device after it is dry.
- Plastic bag should not be cleaned but should be replaced every 4 weeks or as needed.

all devices, including Diskus, the drug powder is exposed when the device is activated.^{74,86} In addition, all DPIs are affected by exhaled air introduced into the mouthpiece, especially after the device is loaded and when the powder is exposed. Therefore, patients must be instructed to exhale away from the DPI before inhalation.²⁷

Clinical Efficacy. DPIs have been shown to be equivalent in efficacy to pressurized pMDIs.^{87,88} The need to replace CFC-propelled MDIs has given renewed impetus to the development of DPI technology. In evidence-based guidelines, Dolovich et al.⁶⁹ found that a DPI is just as good as a pMDI when selecting a device for inhaled medication in the outpatient setting. It is stressed that selection should be based on the patient's knowledge and understanding of the device's use (Box 3.10).

Selecting an Aerosol Device

Several important questions arise concerning aerosol devices. How should they be quantitatively described for clinicians? Are there differences in clinical effect with different devices, including spacer and reservoir accessories? What is the correct or optimal use of different types of devices? With all aerosol delivery devices, respiratory care personnel should carefully review instructional materials and package inserts to train patients in their correct use. Knowledge of aerosol delivery devices by medical personnel, together with the ability to teach patients in the correct use of devices, is necessary for effective drug delivery. Respiratory care practitioners have been shown to receive formal education in the use of various aerosol devices more often compared with nursing

• BOX 3.9 Advantages and Disadvantages of Dry Powder Inhaler Devices

Advantages

- Small and portable
- Short preparation and administration times
- Breath actuation; no need for hand-breathing coordination
- No inspiratory hold or head tilt needed
- No CFC propellants (environmentally friendly)
- No cold Freon effect to cause bronchoconstriction or inhibit full inspiration
- Simple determination of remaining drug doses
- Built-in dose counter

Disadvantages

- Only a limited range of drugs is available to date.
- Patients are not as aware of the dose inhaled as with an MDI and may distrust delivery.
- Moderate to high inspiratory flow rates are needed for powder dispersion.
- Relatively high oropharyngeal impaction and deposition can occur.
- Some devices, such as the Aerolizer, are single-dose devices and must be loaded before each use.
- Vulnerable to ambient humidity or exhaled humidity into mouthpiece.
- Different DPI needed with different drugs.
- Easy for patient to confuse directions for use with other devices.

CFC, Chlorofluorocarbon; DPI, dry powder inhalers; MDI, metered dose inhaler.

Modified from Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.

staff or physicians. Knowledge and demonstration scores with an MDI, reservoir device, and DPI were higher for RTs than for registered nurses or physicians in a study by McIvor et al.⁸⁹ Dolovich et al.⁶⁹ recommended that the following eight questions be asked when selecting an aerosol device:

1. In what devices is the desired drug available?
2. What device is the patient likely to be able to use properly, given age and clinical setting (e.g., home, hospital)?
3. For which device and drug combination is reimbursement available?
4. Which device is least expensive?
5. Can you use the same device for all inhaled drugs that the patient is taking?
6. Which device is the most convenient one for the patient or family?
7. How durable is the device?
8. Does the patient or practitioner have a specific device preference?

Clinical Application of Aerosol Delivery Devices

With so much information available, it is often difficult to decide what is best for patients. Dolovich et al.⁶⁹ conducted an overview of all pertinent literature to develop recommendations for the clinical use of aerosol devices. The following sections summarize their findings.

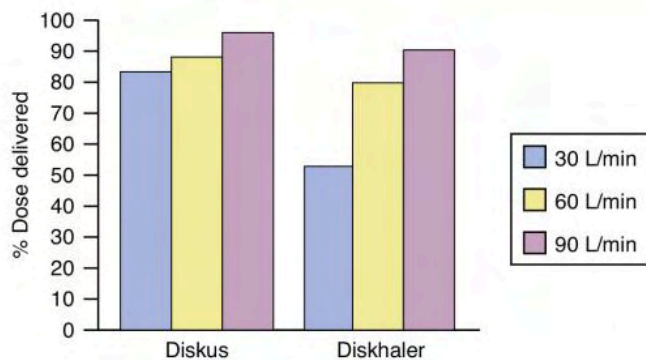
Recommendations Based on Clinical Evidence

Aerosol Delivery of Short-Acting β_2 Agonists in the Emergency Department

An MDI with a holding chamber and a nebulizer were equally effective in the treatment of adult and pediatric patients in the emergency department. Both modes of delivery improved



• **Fig. 3.23** Dry powder inhalers (DPIs) available in the United States. **A**, Unit-dose DPI: Aerolizer (Novartis, East Hanover, New Jersey). **B**, Handihaler (Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut). **C**, Multiple unit-dose DPI: Diskhaler (GlaxoSmithKline, used with permission). **D**, Flexhaler (AstraZeneca LP, Wilmington, Delaware). **E**, Multiple-dose DPI: Diskus inhaler (GlaxoSmithKline, used with permission). **F**, Twisthaler (Merck & Co Inc.). **G**, Neohaler. **H**, Ellipta. **I**, Pressair. **J**, TOBI Podhaler. (**A**, The FORADIL AEROLIZER photo image is reproduced with permission of Schering Corporation, subsidiary of Merck & Co., Inc. All rights reserved. FORADIL is a registered trademark of Astellas Pharma, Inc. and the trademark of AEROLIZER is a registered trademark of Novartis AG. **F**, The ASMANEX TWISTHALER photo image is reproduced with permission of Schering Corporation, subsidiary of Merck & Co., Inc. All rights reserved. ASMANEX and TWISTHALER are registered trademarks of Schering Corporation.)



• **Fig. 3.24** Effect of inspiratory flow rate on the percentage of nominal dose delivered by three dry powder inhaler devices. Data were derived in vitro for albuterol. (Modified from Prime, D., Grant, A. C., Slater, A. L., et al. [1999]. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurized MDI, Diskus inhaler, Diskhaler, and Turbuhaler. *Journal of Aerosol Medicine*, 12, 75.)

• BOX 3.10 Use of Dry Powder Inhalers

Specific instructions for use of the various DPIs currently available should be reviewed on the package insert before use or patient education.

Generic Recommendations That Apply to All DPIs

1. Read and follow instructions of each DPI for proper assembly.
2. Keep DPI in proper orientation during treatment.
3. Ensure mouthpiece is clear of all foreign matter.
4. Exhale normally *away from the DPI* because humidity reduces inhaled dose.
5. Inhale from mouthpiece forcefully to total lung capacity.
6. Hold breath up to 10 seconds or as long as possible.
7. Remove from mouth and exhale away from device.
8. Track doses remaining in the DPI after each use.

Manufacturers' recommendations for use are summarized for the unit-dose DPI (Aerolizer, Neohaler, Podhaler, and Handihaler), multiple unit-dose DPI (Diskhaler), and multiple-dose DPI (Diskus, Twisthaler, Flexhaler, Pressair, and Ellipta). As new devices become available in the United States, package inserts will provide instructions for use.

Critical Steps in Use of Unit-Dose DPI

Use of Aerolizer or Neohaler

1. Remove mouthpiece cover.
2. Hold base of inhaler and twist mouthpiece counterclockwise.
3. Remove capsule of medication from package, and place in base of inhaler (remove capsule immediately before use; do not store in inhaler).
4. Hold base of inhaler and twist clockwise to close.
5. Two buttons are on sides of inhaler; press simultaneously to pierce capsule.
6. Exhale *away from inhaler* to functional residual capacity or residual volume.
7. Keep head in upright position, and hold device horizontally with lips sealed around mouthpiece.
8. Breathe in as deeply as possible, holding breath for about 10 seconds if possible. Breathe out slowly, away from device.
9. Open the inhaler to expose the chamber. Examine the capsule, and if powder remains, repeat inhalation. If powder has been completely used, dispose of capsule.
10. Close mouthpiece, and replace cover.

Use of HandiHaler

1. Before using device, open foil package and remove capsule (remove capsule immediately before use; do not store in inhaler).
2. Pull dust cap upward to open.
3. Open mouthpiece, and place capsule in chamber.
4. Close mouthpiece firmly until you hear it click; leave dust cap open.

symptoms and lung function. There is little information to show that a DPI is as effective as an MDI with a holding chamber or a nebulizer for delivery of short-acting β_2 agonists.

Aerosol Delivery of Short-Acting β_2 Agonists in the Hospital

There was no significant difference in lung function among inpatients treated with either an MDI with a holding chamber or a nebulizer. Reliable studies examining outcomes among inpatients treated with DPIs are lacking. At present, it is better to use an MDI with a holding chamber or a nebulizer to deliver short-acting β_2 agonists.

Intermittent Versus Continuous Nebulizer Delivery of β_2 Agonists

There is no difference in effect between intermittent and continuous nebulizer delivery of short-acting bronchodilators. Specifically, there is no change in lung function, asthma scores, or incidence

5. Hold device with mouthpiece up, and press piercing button once to release medication.
6. Exhale *away from inhaler* to functional residual capacity or residual volume.
7. Place mouthpiece into mouth, and close lips tightly around mouthpiece.
8. Breathe in slowly at a rate sufficient to hear capsule vibrate until lungs are at total lung capacity; hold breath for about 10 seconds, if possible. Breathe out slowly, away from device.
9. To ensure entire dose has been inhaled, repeat steps 6 through 8.
10. Open mouthpiece, tip out capsule, and throw it away.
11. Close mouthpiece and replace dust cap for storage.

Use of Podhaler

1. Hold base of Podhaler, and unscrew lid in a counterclockwise direction; set lid aside.
2. Stand Podhaler upright in base of case.
3. Hold body of Podhaler, and unscrew mouthpiece in a counterclockwise direction, setting aside mouthpiece on a clean, dry surface.
4. Take blister card, and tear precut lines along length and width.
5. Peel foil that covers Podhaler capsule on blister card.
6. Remove capsule, and place in capsule chamber at top of Podhaler.
7. Place mouthpiece back on Podhaler, and screw mouthpiece in a clockwise direction until tight.
8. Hold Podhaler pointing mouthpiece down.
9. Place thumb on blue button, and press the blue button all the way down once.
10. Exhale *away from inhaler* to functional residual capacity or residual volume.
11. Place mouthpiece into mouth, and close lips tightly around mouthpiece.
12. Breathe in slowly until lungs are at total lung capacity; hold breath for about 5 seconds if possible; breathe out slowly, away from device.
13. To ensure entire dose has been inhaled, repeat steps 10 through 12.
14. Unscrew mouthpiece, remove capsule from chamber, and throw away capsule.
15. Repeat steps 4 through 14 three more times until all four doses (four capsules) have been used.

Critical Steps in Use of Multiple Unit-Dose DPI²⁷

Use of Diskhaler

1. Remove cover of Diskhaler and ensure that device and mouthpiece are clean.
2. Extend tray, and push ridges to remove tray.
3. Load medication disk on rotating wheel.
4. Pull cartridge all the way out, and then push it all the way in until you see medication disk in dose indicator.

• BOX 3.10 Use of Dry Powder Inhalers—cont'd

5. Keep device flat and lift back of lid until it is lifted all the way up to pierce the medication blister.
6. Click back into place.
7. Move Diskhaler away from mouth, and breathe out as much as possible.
8. Place the mouthpiece into mouth.
9. Ensure that air hole on mouthpiece is not blocked.
10. Inhale as quickly and deeply as possible.
11. Move Diskhaler away from mouth and hold breath for 10 seconds or as long as possible.
12. Exhale slowly.
13. If another dose is needed, pull cartridge out all the way, and then push it back in all the way so that next blister can be moved into place; repeat steps 5 through 12.
14. Place mouthpiece cover back on after treatment. Keep remaining blisters sealed until inspiration to protect from humidity and loss.

Critical Steps in Use of Multiple-Dose DPI

Use of Diskus Inhaler

1. Push thumbgrip away from you to expose mouthpiece.
2. Hold Diskus in a level (horizontal) position, slide lever next to mouthpiece away from you until it clicks.
3. Hold Diskus level and exhale *away from mouthpiece*.
4. Put mouthpiece to lips, and inhale steadily and deeply through Diskus.
5. Remove Diskus from mouth, hold breath for about 10 seconds if possible, and breathe out slowly *away from device*.
6. Close mouthpiece cover by sliding thumbgrip back toward you.
7. Rinse mouth with water when using a corticosteroid.
8. Do not wash any part of device; keep it dry.

Use of Flexhaler²⁷

1. Twist and lift off cover.
2. Hold mouthpiece of Flexhaler up while loading a dose.
3. Do not hold mouthpiece while inhaler is loaded.
4. Twist brown grip in one direction as far as it goes, regardless of the way you turn it first.
5. Twist grip back in the other direction completely.
6. Listen carefully for a click during each of the twisting movements.
7. Do not exhale *into* device.
8. Place mouthpiece in mouth, seal mouthpiece with lips, and inhale deeply and forcefully through inhaler.
9. Remove inhaler from mouth, and hold breath for 10 seconds or as long as possible.
10. Exhale, but do not blow, *into* mouthpiece.
11. If more than one dose is required, repeat steps 2 through 10.
12. Put cover back on inhaler, and twist shut.
13. Rinse mouth with water after each dose to reduce risk of developing thrush; do not swallow rinsing water.

DPI, Dry powder inhaler.

Use of Pressair

1. Remove protective cap by squeezing arrows marked on each side of cap and pulling out.
2. Hold Pressair outside of mouth, mouthpiece facing you, green button facing straight up.
3. Press green button all the way down before inserting into mouth.
4. Check control window to make sure color has turned from red to green, which means that dose is ready; if not repeat step 3 until control window turns green.
5. Exhale completely, not exhaling *into* inhaler.
6. Place mouth around mouthpiece and inhale until a click is heard, continuing to inhale all the way even after click is heard.
7. Remove inhaler from mouth, and hold breath for as long as possible.
8. Exhale, but do not blow, *into* mouthpiece.
9. Check to make sure control window has turned red, which means that dosing was successful; if not, repeat steps 5 through 9.
10. When done, return cap to mouthpiece.

Use of Ellipta

1. Slide cover down until a click is heard and mouthpiece is exposed.
2. Holding inhaler away from mouth, exhale completely, but not *into* inhaler.
3. Place mouth around mouthpiece, and inhale, being careful to not block air vent.
4. Remove inhaler from mouth, and hold breath for 3 to 4 seconds or as long as possible.
5. Exhale, but not blow, *into* mouthpiece.
6. When done, slide cover over mouthpiece as far as it will go.

Common Errors in Use²⁷

- Not inhaling correctly
- Failure to pierce or open drug package
- Using the inhaler in wrong orientation
- Failure to prime
- Exhaling into inhaler at any point in process
- Not exhaling to residual volume before inhalation
- Not inhaling forcefully enough
- Covering inhalation vents
- Inadequate or no breath hold
- Exhaling through mouthpiece after inhalation

Cleaning Instructions: Dry Powder Inhaler

The DPI should not be washed and submerged in water because moisture decreases drug delivery. If necessary, the mouthpiece may be wiped with a dry cloth. Each manufacturing company recommends periodic cleaning and suggests wiping the mouthpiece of the DPI with a clean, dry cloth.²⁷

of adverse effects when comparing the two delivery methods. It has been noted that the time required for staff to maintain and administer a continuous aerosol is less than that required with an intermittent nebulizer.

Aerosol Delivery of β_2 Agonists to Patients Receiving Mechanical Ventilation

The quality of evidence concerning the administration of bronchodilators to patients receiving mechanical ventilation is fair. There seems to be no difference in effect, regardless of a nebulizer or an MDI with a holding chamber being used to deliver bronchodilators to adults or children who are mechanically ventilated.

Concerning patients receiving noninvasive ventilation, there is little evidence to suggest which formulation is superior. In any case, with invasive ventilation and noninvasive ventilation, the technical factors for delivering an aerosolized agent have changed dramatically.

Aerosol Delivery of Short-Acting β_2 Agonists for Asthma in the Outpatient Setting

Among outpatients using either an MDI (with or without a holding chamber) or a DPI, there seems to be no difference in effect on lung function and asthma symptoms. However, the need for a holding chamber is evident; the literature favors the use of this

device. Little research has been done on the use of nebulizers in the outpatient setting. Selection of the most appropriate aerosol device for outpatients must be made on a case-by-case basis.

Delivery of Inhaled Corticosteroids for Asthma

Whether an MDI with a holding chamber or a DPI is used, symptom scores and lung function remain the same among adult patients with asthma treated with inhaled corticosteroids.

Delivery of β_2 Agonists and Anticholinergic Agents for Chronic Obstructive Pulmonary Disease

Evidence gathered in the treatment of patients with COPD shows no difference in effect whether a nebulizer, an MDI with or without a holding chamber, or a DPI is used. Selection of the proper aerosol device depends on numerous factors.

Factors to Consider

There are many factors to consider when selecting the proper aerosol device:

- Patient or clinical preference
- Convenience of device
- Practicality of device
- Durability of device
- Cost and reimbursement
- Drug availability
- Ability of all prescribed drugs to be delivered by same device

After these factors have been addressed and selection has taken place, it is important to educate the patient properly. Education of the patient cannot take place until proper education of the RT has been completed.

Lung Deposition and Loss Patterns With Traditional Aerosol Devices

KEY POINT

A traditional aerosol device delivers approximately 10% to 15% of the total dose to the airway. Because total dose amounts differ among the various types of devices for the same drug, these devices do not necessarily deliver equivalent amounts of drug. Newer aerosol devices, as well as some still in development, are more efficient, with resultant lung depositions of 30% to 50% or greater. This improved efficiency in lung delivery will necessitate dose modifications.

Aerosol devices that have traditionally been used in respiratory care deliver approximately 10% to 15% of the total drug dose to the lung. The pattern of loss to the mouth, stomach, and digestive apparatus and through exhalation differs among the device types. Fig. 3.6 shows the percentage of dose deposited in the lung and the pattern of loss with drug delivery systems that have traditionally been used in respiratory care: an MDI, an MDI with a spacer, an SVN, and a DPI.

Some of the lung deposition data presented in Fig. 3.6 are summarized in the following list, along with information from additional studies, including one comparing CFC and HFA formulations. The percentage of lung deposition is much greater with the HFA formulation.

- MDI (CFC, technetium 99m [^{99m}Tc]-labeled Teflon): 8.8%⁹⁰
- MDI (HFA, ^{99m}Tc label): 53%⁹¹
- MDI and spacer (CFC, ^{99m}Tc -labeled Teflon and InspirEase; Schering Corp., Kenilworth, New Jersey): 14.8%⁹²

- SVN (^{99m}Tc label; Inspiron Mini-Neb, Bard International of Sunderland, England): 12.4%⁹³
- DPI (Turbuhaler): 14.8% to 27.7%⁹⁴

MDIs and SVNs show the greatest contrast in the loss pattern of aerosol drug. Most of the loss with an MDI occurs in the mouth and stomach (approximately 80%). The loss with an SVN is primarily in the delivery apparatus (66%), with most of that remaining in the nebulizer, whereas an MDI loses approximately 10% in the actuator.

Adding a spacer or holding chamber to an MDI reduces the amount of drug lost in the oropharynx and in the stomach.⁹⁵ The DPI is similar to the MDI in its pattern of aerosol loss.

Equivalent Doses Among Device Types

If traditional MDI, SVN, and DPI devices all deliver approximately the same percentage of total device dose to the lungs, with the exception of HFA formulations, and the nominal dose in the devices differs, then different amounts of drug are placed within the lung. For example, the dose of albuterol, a β -adrenergic bronchodilator, by MDI versus nebulizer is as follows:

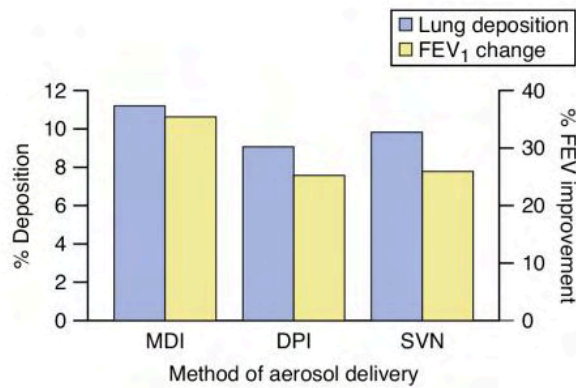
- MDI: 2 puffs, or 0.2 mg (200 mcg)
- SVN: 0.5 cc, or 2.5 mg (2500 mcg)

The ratio of MDI to SVN dose is approximately 1:12. If approximately 10% of the dose reaches the lungs, very different doses are being delivered from these aerosol devices. For example, if we assume that 10% of an albuterol dose reaches the lungs when administered via an MDI and an SVN, then a lung dose of 20 mcg would be given via the MDI versus a lung dose of 250 mcg from the SVN (10% of 200 mcg versus 10% of 2.5 mg). Several studies have examined this question of equipotent doses between delivery devices. An equipotent dose is the dose by each delivery method that produces an equivalent degree of effect (for bronchodilators, this would be bronchodilation).

The standard difference in dose between the MDI and SVN delivery methods for albuterol is in the ratio of 1:12. However, at least two studies suggest MDI/SVN dose ratios of 1:3 and 1:4 to achieve equal bronchodilation or equivalent amounts of drug delivery to the lung.^{96,97} An equipotent dose ratio of 1:3 or 1:4 is achieved by increasing the number of puffs from the MDI to 7 or 10 in the two studies.

One of the clearest statements on the question of delivery efficiency among traditional aerosol devices resulted from the study by Zainudin et al.⁹⁸ This study examined drug delivery by pMDI (CFC propellants), DPI (Rotahaler), and gas-powered SVN (Acorn). The results are particularly helpful because the investigators used the same dose of 400 mcg of albuterol (salbutamol) in each of the device types; this allowed for a direct microgram-for-microgram comparison of the dose from the devices. The percentage of lung deposition is shown in Fig. 3.25, with an MDI delivery of 11.2%, a DPI delivery of 9.1%, and an SVN delivery of 9.9%.

The clinical response, measured as the improvement in FEV_1 , is also similar, although the change with the MDI (35.6%) is statistically significantly greater than that seen with the DPI (25.2%) or the SVN (25.8%), a result not well explained in the study. These results support the view that the amount of aerosol drug delivered to the lung is similar with any of the three device types, and the clinical response is similar. The amount of bronchodilation obtained is a reflection of the dose of drug given and not the method of delivery.^{99,100} As discussed in the following section, the



• **Fig. 3.25** Lung deposition and clinical response: comparison of three bronchodilator delivery methods. Shown are lung deposition (as percentage of total dose) and clinical response (percent improvement in forced expiratory volume in 1 second [FEV₁]) after aerosol delivery of the same dose of albuterol (400 mg) from three types of aerosol devices. (Data from Zainudin, B. M., Biddiscombe, M., Tolfree, S. E., et al. [1990]. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurized metered dose inhaler, as a dry powder and as a nebulized solution, *Thorax*, 45, 469).

development of aerosol devices that are highly efficient for lung delivery of a drug is likely to lead to changes in recommended doses. For example, the increased efficiency of MDI HFA-propelled beclomethasone, cited in the section on HFA propellants, has resulted in the use of half the dose normally found with MDI CFC-propelled beclomethasone, with equivalent effects. These changes will affect what constitutes equivalent doses between different types of devices.

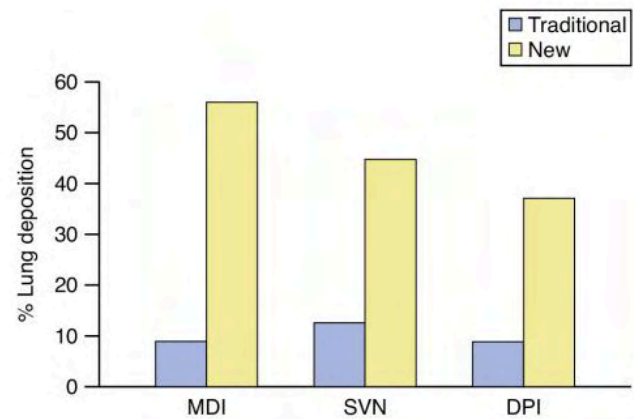
Lung Deposition With Newer Aerosol Devices

The development of increasingly efficient devices compared with older MDIs, SVN, and DPIs will cause the traditional figures of 10% to 15% for lung deposition to be revised upward. Unless newer devices completely replace the older, traditional aerosol generators used clinically, there will be a wide variety of lung depositions seen, rather than a single range of 10% to 15%. The amount of lung delivery will depend on which device is used. Fig. 3.26 graphically compares lung deposition with traditional devices (MDIs, SVN, and DPIs) with lung deposition with newer devices. These data have been compiled from several studies and for various drugs.^{101–103}

One implication of changing and increasing lung deposition amounts is that the total dose from a device must be reduced. With a greater percentage reaching the lung, a lower total dose is needed from the device. Without proportional reduction in total device dose, toxic effects would be possible. Ultimately, the important factor is not the device per se, but rather the amount of drug reaching the lungs when treating pulmonary disease.

Clinical Equivalence of Metered Dose Inhalers and Nebulizers

It is still relatively common in clinical practice to use an SVN instead of an MDI in emergent acute situations requiring aerosol bronchodilator delivery. However, a large and growing body of evidence indicates that an MDI with a spacer or holding chamber is as effective as an SVN in acute airway obstruction. An MDI with a reservoir has been shown to be as effective as an SVN in the treatment



• **Fig. 3.26** Comparison of lung deposition with older traditional aerosol devices (traditional metered dose inhaler [MDI], chlorofluorocarbon-MDI; traditional small volume nebulizer [SVN], Inspiron MiniNeb; traditional dry powder inhaler [DPI], Rotahaler) and with newer devices (new MDI, hydrofluoroalkane-beclomethasone¹⁰³; new SVN, Respimat¹⁰²; new DPI Spiros¹⁰¹).

of all age groups, from nonventilated preterm infants (with addition of a face mask) to adult patients in emergency departments Table 3.4.^{104–107} summarizes selected studies supporting the clinical equivalence of either an MDI or an SVN in emergency treatment for various age groups. Amirav and Newhouse¹⁰⁸ published a comprehensive review of studies on this issue. A meta-analysis of studies comparing bronchodilator administration by MDI or “wet nebulizer” (i.e., SVN) concluded that either method was equivalent in the treatment of acute airflow obstruction in adults.¹⁰⁹

Age Guidelines for Use of Aerosol Devices

It cannot be assumed that every patient can correctly use each type of delivery device. The differences, in particular, the relative advantages and disadvantages of the available devices, can be used as the basis for choosing which type of device best matches a patient’s needs. Age is an important factor to consider when selecting an aerosol delivery system. Age guidelines have been provided in the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR 3)¹¹⁰ and are listed in Table 3.5. A consideration that applies to the final decision is discussed by Dolovich et al.⁶⁹

Patient–Device Interface

KEY POINT

The *patient–device interface* is another variable in aerosol delivery to the lung and includes administration of *intermittent positive-pressure breathing (IPPB)*; administration of the face mask; and delivery to intubated, ventilated patients, which is complicated by numerous variables.

Most aerosol drug administration is through oral inhalation; that is, the subject inhales the aerosol through the open mouth. However, other types of interface occur in clinical practice and raise questions concerning efficacy and drug delivery. These include positive-pressure aerosol administration with a face mask and administration of aerosolized drugs through ETTs.

TABLE 3.4 Studies Showing Equivalence of Metered Dose Inhaler With Reservoir or Face Mask to Small Volume Nebulizer for Bronchodilator Administration in Acute Airflow Obstruction for Various Age Groups

Age Group	Drug	Dosage	Outcome Variables	Reference
Preterm infants, 47 ± 4.8 days	Albuterol*	MDI/spacer/mask: 2 puffs (200 mcg) q4h SVN/mask: 0.2 mg × (200 mcg) q4h	Lung compliance, resistance	Fok et al. ¹⁰⁴
Infants, 16 ± 15 months	Albuterol	MDI/HC/mask: 4 puffs (400 mcg) q20min × 3 SVN: 2.5 mg q20min × 3	Respiratory rate, clinical scores, admissions	Mandelberg et al. ¹⁰⁵
Children, 5-16 years	Terbutaline	MDI/HC/mask: 3 puffs (0.75 mg) × 1 SVN/mouthpiece: 0.5 mL (2.5 mg) × 1	Lung function, clinical scores	Lin and Hsieh ¹⁰⁶
Adults, 64.6 ± 13.3 years	Albuterol	MDI/HC: 2 puffs (200 mcg) q15min × 3 SVN: 0.5 mL (2.5 mg) q15min × 3	Spirometry, asthma scores	Mandelberg et al. ¹⁰⁸

*Albuterol is also known as salbutamol outside the United States.

HC, Holding chamber (valved reservoir); MDI, metered dose inhaler; spacer, nonvalved reservoir; SVN, small volume nebulizer.

TABLE 3.5 Age Guidelines for Use of Aerosol Delivery Devices

Aerosol System	Age
SVN	≤2 years
MDI	>5 years
MDI with reservoir	>4 years
MDI with reservoir/mask	≤4 years
MDI with ETT	Neonate and older
Breath-actuated MDI	>5 years
DPI	≥5 years

DPI, Dry powder inhaler; ETT, endotracheal tube; MDI, metered dose inhaler; SVN, small volume nebulizer.

Data from National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, National Institutes of Health: National Asthma Education and Prevention Program, Expert Panel Report 3: *Guidelines for the Diagnosis and Management of Asthma*, NIH Publication 08-4051. (2007). Bethesda, Maryland: National Institutes of Health.

Administration by Intermittent Positive-Pressure Breathing

Although administration through IPPB has been a popular form of aerosol therapy, the consensus of research on this method of delivery is that IPPB delivery of aerosolized medication is no more clinically effective than simple spontaneous, unassisted inhalation from SVNs.^{111–113} Consequently, if the patient is able to breathe spontaneously without mechanical support, the use of IPPB for delivery of aerosolized drugs is not supported for general clinical or at-home use.

CLINICAL CONNECTION

The respiratory therapist should prioritize using a mouthpiece over a mask. The use of a mask can decrease aerosol delivery by 50% or more.

Face Mask and Blow-by Administration

A face mask with an aerosol generator usually is applied in infants and young children or in debilitated, unresponsive patients. The clinical efficacy of a face mask in a pediatric application has been shown by Restrepo et al.⁴⁴ and by Lin et al.¹¹⁴ Lowenthal and Katan¹¹⁵ compared face mask and mouthpiece delivery of nebulized albuterol in children and adolescents ages 6 to 19 years for emergency department treatment of acute asthma. Their study found that face mask administration did not significantly improve lung function measures, even in patients with nasal congestion. They speculated that congested nasal passages caused mouth breathing while using the mask. Greater tremor was observed with the face mask group, implying a higher systemic level of drug compared with patients using a mouthpiece.

Lung deposition of drug has also been measured for mouthpiece and face mask administration of aerosol drugs. Most of the available data are for infants and children because this age group is most likely to be treated via a face mask or blow-by for aerosol delivery. Because the use of a mask demonstrates questionable results, the use of blow-by provides negligible results. Blow-by is not recommended for any use.¹¹⁶

Mechanical Ventilation Administration

Aerosolized drug delivery commonly occurs with intubated neonatal and adult patients during mechanical ventilation. Data quantifying the efficiency of aerosol administration during mechanical ventilation have been summarized in a review by Gardenhire.¹¹⁷ Evaluation of aerosol delivery is complicated by the number of variables introduced if the patient is receiving mechanical ventilation and by the difficulty in quantifying drug delivery accurately. Box 3.11 lists the many variables of administration of an aerosol drug through an ETT to ventilated patients. The effect of some of these variables, with SVN, VMN, and MDI aerosol administration, has been investigated. The following list summarizes the state of knowledge presented by Gardenhire¹¹⁷ and Duarte.¹¹⁸

- Spontaneous breathing modes provide more aerosol compared with other controlled ventilator modes.

• BOX 3.11 Summary of Variables Present in Aerosol Delivery to Intubated, Mechanically Ventilated Critical Care Patients

Ventilator

- Nebulizer power system
- Duty cycle (flow, volume, rate)
- Inspiratory flow pattern
- Mode of ventilation
- Breath modifications (PEEP, inflation hold)
- Spontaneous, assisted, or controlled breaths
- Humidification and temperature
- Position of generator in circuit
- Size of ETT

Aerosol Generator

Small Volume and Vibrating Mesh Nebulizer

- Volume of fill
- Type of solution
- Brand of SVN
- Intraproduct reliability
- Continuous versus intermittent
- Flow rate

Metered Dose Inhaler

- Timing of actuation
- Use and design of reservoir device
- Type of drug used

ETT, Endotracheal tube; PEEP, positive end-expiratory pressure; SVN, small volume nebulizer.

- In an adult, a minimum of 500 mL tidal volume is needed to provide efficacious aerosol delivery.
- The lower the flow, the more effective is the aerosol delivery.
- Sinusoidal and descending wave forms have better aerosol delivery compared with square forms.
- A heat and moisture exchanger (HME) should be bypassed when delivering aerosolized agents.
- Heat and humidity decrease aerosol particle delivery to the lungs.
- The literature makes note that a reduction in humidity may increase the number of inhaled particles, but because some nebulizers require a longer time to nebulize, disconnecting a circuit to bypass the humidifier could lead to increased risk of ventilator-associated pneumonia.
- The diameter of the tube plays a role in the impaction of aerosol particles. The narrower the tube (e.g., in pediatrics), the lower is the percentage of drug that is delivered to the patient.
- The use of a less dense gas, such as a helium–oxygen mixture (heliox), can increase particle deposition.
- Both an MDI and a nebulizer can be used effectively in administering inhaled agents to a patient receiving mechanical ventilation.
- To improve aerosol delivery, an SVN should be placed after the humidifier, but as close to the ventilator and away from the circuit Y, instead of between the circuit Y and the ETT.
- VMNs can be placed before the humidifier.
- VMNs and MDIs are effective 6 inches from the circuit Y.
- When using an MDI, timing the actuation of the aerosol device with precise inspiration by the ventilator may increase drug delivery by 30%.

- The application of a breath hold may provide additional drug delivery.

The use of HFA-MDIs may increase the amount of drug to the intubated patient. Mitchell et al.¹¹⁹ found that the emitted dose of an HFA-MDI was almost six times greater than that of a CFC-MDI.

Adjunct Systems for Aerosol Therapy

Adjunct systems also allow for administration of aerosol therapy through high-flow nasal cannula (HFNC). A secondary adapter (T-connector) can allow for administration of mesh nebulizers to patients on an HFNC.¹²⁰ Perry et al. found that more than 60% of the nebulizer dose (Albuterol) in an HFNC mesh nebulizer model in vitro was actually deposited in the adapter rather than reaching the patient.¹²¹ A trans-nasal aerosol delivery device is also used as an adjunct adapter for aerosol delivery via nasal route.¹²² This trans-nasal pulmonary aerosol delivery (tPAD) device is developed to deliver a constant aerosol output of 2 mL/hour from a nasal cannula primarily for administration overnight to patients.¹²² Research has shown that the tPAD achieves a 39% pulmonary deposition, similar to an oral jet nebulizer.¹²² This adapter is helpful for patients with a need for passive aerosol therapy, including cystic fibrosis patients.¹²⁰

Technological Adjuncts for Aerosol Therapy

Several mobile applications and inhaler sensors provide an opportunity for patients to track their medication dosage, timing, and provide feedback on inhaler technique.¹²³ Propeller Health developed a platform for tracking inhaler administration via a digital health application and inhaler sensors.¹²³ This system, compatible with many MDIs, including the Novartis' Breezhaler and GlaxoSmithKline's Diskus and Ellipta.¹²³ This specific technological interface resulted in a 78% reduction in rescue inhaler use and an improvement in symptom-free days among asthmatic patients in one study.¹²⁴

Another mobile application, the Hailie™, also provides reminders for medication usage.¹²³ Chan and colleagues found that this digital application resulted in improved medication adherence (by 180%) and reduced rescue inhaler usage (by 45%).¹²⁵

Recommendations for the COVID-19 Pandemic

KEY POINT

Exposure to contaminated aerosols from COVID-19 patients is a serious concern for health care professionals and other individuals. Providers should utilize MDIs for mild COVID-19 for individuals capable of effective MDI administration.

The risk of COVID-19 exposure from fugitive aerosols is a major concern amidst the current COVID-19 pandemic for health care workers. Recommendations for optimizing patient treatment and minimizing exposure to COVID-19 among health care providers include providing MDIs to patients with mild COVID-19 who are capable of effective MDI administration.¹²⁶ Mesh nebulizers are also preferred over jet nebulizers for ventilated patients with severe COVID-19, since mesh nebulizers eliminate the need for breaking the ventilator circuit and risking exposure of COVID-19. Additionally, mesh nebulizers provide a better alternative to MDIs, which also require breaking the ventilator circuit. Mesh nebulizers can provide the optimal amount of drug deposition to the patient, especially when paired with providing an adequately timed inspiratory hold and proper placement of the jet nebulizer.¹²⁶

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What are the three most common aerosol-generating devices used to deliver inhaled drugs?
2. Describe the inspiratory pattern you would instruct a patient to use with an MDI.
3. What are three advantages offered by a reservoir device used with an MDI?
4. Would a DPI be appropriate for a 3-year-old child with asthma?
5. What is meant by the term *dead volume* in an SVN?
6. What are the optimal filling volume and the power gas flow rate to use with an SVN?
7. How does the electrostatic charge affect an MDI when used with a holding chamber?
8. Which device would be better to deliver a β agonist to an adult patient in the emergency department—SVN, MDI, or DPI?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 17-year-old boy with a history of allergic asthma is given a prescription for MDI albuterol, a bronchodilator used as a rescue agent. The HFA formulation of albuterol (Proventil HFA) is prescribed. After using the MDI a few times, the patient complains to you that even though he can feel that there is drug in the canister when he shakes it before using, it feels as if “very little spray” is coming out when he inhales a puff. He believes the MDI is not functioning properly and that he is not getting the regular inhaled dose.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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4

Calculating Drug Doses

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CHAPTER OUTLINE

Systems of Measure

Metric System
International System of Units
Household Units of Measure

Calculating Doses From Prepared-Strength Solutions

Calculating With Proportions
Drug Amounts in Units
Calculations With a Dosage Schedule
Additional Examples: Prepared-Strength Drugs

Calculating Doses From Percent-Strength Solutions

Types of Percent Preparations
Weight to Weight

Weight to Volume

Volume to Volume

Solutions by Ratio

Ratio by Grams to Milliliters

Ratio by Simple Parts

Solving Percent-Strength Solution Problems

Summary

Quantity Sufficient

Percent Strengths in Milligrams per Milliliter

Diluents and Drug Doses

Additional Examples: Solutions

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms pertaining to calculating drug dose
2. Use the metric system
3. Calculate drug doses using proportions
4. Calculate drug doses using percent-strength solutions

KEY TERMS AND DEFINITIONS

Percent Part of the active ingredient that is in a solution containing 100 parts.

Schedule Amount of drug that is needed on the basis of a patient's weight.

Solute Substance or active ingredient that is dissolved in a solution.

Solution Physically homogeneous mixture of two or more substances.

Solvent Substance, usually a liquid, used to make a solution.

Strength Amount of solute in a solution; usually expressed as a percentage.

Respiratory therapists are highly skilled health care providers who work in many different areas with other health care providers. Demonstrating a general knowledge of drug dosing has positive effects on all patients. Chapter 4 presents calculations of drug doses. Systems of measure are reviewed briefly. Dose calculations from prepared-strength formulations such as liquids, tablets, and capsules are presented with examples. Calculations of doses from solutions whose concentrations are expressed as percent strength, along with intravenous dose calculations, are presented with examples. Practice problems and answers are included.

Systems of Measure

Metric System

KEY POINT

Drug calculations use the metric system of measure.

Table 4.1 provides metric units of measures for length, volume, and weight. Primary units in the metric system are:

Length: Meter

Volume: Liter

Mass: Gram

TABLE 4.1 Metric System of Length, Volume, and Mass (Weight)**Length**

1 kilometer (km)	=	10^3 meters	=	1000 meters
1 hectometer (hm)	=	10^2 meters	=	100 meters
1 decameter (dam)	=	10^1 meters	=	10 meters
1 Meter (m)		Base Unit		1 meter
1 decimeter (dm)	=	10^{-1} meter	=	0.1 meter
1 centimeter (cm)	=	10^{-2} meter	=	0.01 meter
1 millimeter (mm)	=	10^{-3} meter	=	0.001 meter
1 micrometer (μ m)	=	10^{-6} meter	=	0.000001 meter

Volume (Capacity)

1 kiloliter (kL)	=	10^3 liters	=	1000 liters
1 hectoliter (hL)	=	10^2 liters	=	100 liters
1 decaliter (daL)	=	10^1 liters	=	10 liters
1 Liter (L)		Base Unit		1 liter
1 deciliter (dL)	=	10^{-1} liter	=	0.1 liter
1 centiliter (cL)	=	10^{-2} liter	=	0.01 liter
1 milliliter (mL)	=	10^{-3} liter	=	0.001 liter
1 microliter (μ L)	=	10^{-6} liter	=	0.000001 liter

Mass

1 kilogram (kg)	=	10^3 grams	=	1000 grams
1 hectogram (hg)	=	10^2 grams	=	100 grams
1 decagram (dag)	=	10^1 grams	=	10 grams
1 Gram (g)		Base Unit		1 gram
1 decigram (dg)	=	10^{-1} gram	=	0.1 gram
1 centigram (cg)	=	10^{-2} gram	=	0.01 gram
1 milligram (mg)	=	10^{-3} gram	=	0.001 gram
1 microgram (mcg or μ g)	=	10^{-6} gram	=	0.000001 gram
1 nanogram (ng)	=	10^{-9} gram	=	0.000000001 gram
1 picogram (pg)	=	10^{-12} gram	=	0.000000000001 gram

Fractional parts, or multiples of these primary (base) units, are expressed by adding Latin prefixes for sizes smaller than the primary unit and Greek prefixes for sizes larger than the primary unit. Examples of Latin and Greek prefixes found in Table 4.1 are as follows:

Decreasing prefixes (Latin):

Micro = 1/1,000,000
 Milli = 1/1000
 Centi = 1/100
 Deci = 1/10

Increasing prefixes (Greek):

Deca = 10
 Hecto = 100
 Kilo = 1000

In calculating drug doses, the metric units for volume and mass (weight) are needed. A commonly encountered unit of volume in respiratory care pharmacology is the milliliter (mL), or 0.001 liter (L). Common units of weight are kilogram (kg), gram (g), milligram (mg), and, with aerosolized drugs, microgram (μ g, or mcg, as used in this text). Blood levels of drug amounts within the body may be in nanograms per milliliter (ng/mL). Conversions within the metric system should be familiar, such as converting 1 mg to 0.001 g, 500 mL to 0.5 L, or 0.4 mg to 400 mcg. Familiarity with decimal fractions and with the other basic rules of arithmetic is necessary for drug dose calculations.

A gram is defined as the weight of 1 mL of distilled water at 4°C in vacuo. Under these conditions, 1 g of water and 1 mL of water are equal. This, however, should not be used to convert from weight to volume because, depending on the temperature, pressure, and nature of the substance, 1 g of liquid is not always equal to 1 mL of liquid.

Although three different systems of measure have been used in drug calculations, metric units of measure are currently employed with formulations in the United States. Therefore, all of the examples in this chapter are based on the metric system.

International System of Units**KEY POINT**

Volume and weight measures are commonly encountered in pharmacology.

The International System of Units, or *Système International d'Unités* (SI), was adopted in 1960 and is the modern metric system. The SI system is well presented by Chatburn¹ with conversion factors between older metric units for volume and the English system of measurement units. The SI system is based on the meter-kilogram-second (MKS) system, with volume as a derived unit of length. The primary units of interest in pharmacology calculations are as follows:

Mass: Kilogram (kg)

Volume: Cubic meter (m^3)

Although the base unit of measure in the SI system for volume is the cubic meter, the liter and its fractions or multiples are currently accepted in measures of liquid volume:

$$\text{Equivalence: } 10^{-3} m^3 = 1 \text{ L}$$

CLINICAL CONNECTION

In respiratory therapy, most drug doses are expressed in milligrams (mg) or micrograms (mcg). Milligrams are common in liquid aerosol agents that use a nebulizer. Micrograms are often found in metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

Household Units of Measure**KEY POINT**

Household measures (e.g., teaspoon, tablespoon) are also used in the administration of medications.

In general, the metric system of measure is used for drug amounts. However, household measures, such as teaspoons or tablespoons, are used in the administration of medications in the home environment. For example, a cough syrup may have a label giving a usual adult dose as “1 teaspoon every 6 hours.” Household measures are inconsistent—a teaspoon measure may vary from 3 to 5 mL. Although the metric system, which is more exact and consistent with milligrams, micrograms, and milliliters, is recommended in place of household measures, the following equivalences may be helpful. Use of household measures, such as teaspoons, can be very helpful in discussing amounts of substance with a patient.

1 teaspoon = 5 mL = 60 drops
 1 tablespoon = 15 mL = 3 teaspoons
 1 cup = 240 mL = 8 fluid ounces

Calculating Doses From Prepared-Strength Solutions

KEY POINT

The two types of drug calculations include prepared-strength doses and doses from solutions with a concentration expressed as a percentage.

Once the clinician is able to convert freely within the metric system, it is possible to begin calculating drug doses. Calculations generally are of the following two types:

1. Those involving fluids, tablets, or capsules of a given strength (e.g., 5 mg/mL)
 2. Those involving solutions of a percent strength (e.g., 0.5 mL of a 0.5% solution)
- Each type of dose calculation is described separately.

Calculating With Proportions

When using a prepared-strength liquid, tablet, or capsule, you need to determine how much liquid or how many tablets or capsules are required to give the amount, or dose, of the drug ordered. For example, if one tablet of a drug contains 5 mg and you want to give 2.5 mg, half a tablet must be given. The simplest and probably the most accurate, error-free method of calculation when using a vial of a prepared-strength drug (or a tablet or capsule) involves two steps:

1. Convert to consistent units of measure.
2. Set up a straightforward proportion:

$$\frac{\text{Original dose}}{\text{Per amount}} = \frac{\text{Desired dose}}{\text{Per amount}}$$

In step 1, this conversion may be from grams to milligrams within the metric system or from apothecary to metric, if an apothecary dosage strength has been ordered. In step 2, set up the straightforward proportion. Ultimately, you will be solving for an unknown, or x .

Example 1

You have tablets of a drug, each 250 mg in strength. If the patient needs 0.5 g of the drug, how many tablets should be administered?

Solution: If you need 0.5 g of the drug, either convert 250 mg to 0.25 g or convert 0.5 g to 500 mg (preferred). Once the units are consistent, set up the proportion to find the unknown—that is, the number of tablets

needed to deliver the desired dose to the patient. Using the preceding formula,

Original drug dose = 250 mg

Per amount = per tablet

Desired drug dose = 0.5 g = 500 mg

Per amount = unknown

$$\frac{250 \text{ mg}}{1 \text{ tab}} = \frac{500 \text{ mg}}{x \text{ tab}}$$

$$\frac{250 \times x}{250} = \frac{500 \times 1}{250}$$

$$x \text{ tab} = \frac{500}{250}$$

$$x = 2 \text{ tablets}$$

Answer

The amount required is two tablets.

Although this calculation is trivially clear and can be performed mentally, others may require calculation for the sake of accuracy.

Example 2

You have 120 mg of a drug in 30 mL of elixir. How many milliliters of elixir will you use to give a 15-mg dose?

Solution:

$$\frac{120 \text{ mg}}{30 \text{ mL}} = \frac{15 \text{ mg}}{x}$$

Cross-multiplying:

$$120 \text{ mg}(x) = 450$$

Divide both sides by 120 to isolate x :

$$\frac{120 x}{120} = \frac{450}{120}$$

$$x \text{ mL} = 3.75 \text{ mL}$$

Answer

The amount required is 3.75 mL.

Simplification is possible, such as reducing 120 mg/30 mL to 4 mg/mL. Then, because you know that there are 4 mg in every milliliter, simply divide 4 mg/mL into 15 mg to determine how many milliliters are needed. Reducing a liquid to its dosage strength per 1 mL often allows for quick mental computation of the dose. Caution and care should, however, be exercised in the initial reduction. An error at that point will cause a subsequent dosage error. *Do not hesitate to write out a calculation:* Even in a busy clinical setting, a patient's well-being should take precedence over a practitioner's pride in his or her mathematical prowess.

Drug Amounts in Units

KEY POINT

Prepared-strength doses involve calculating how many tablets, capsules, or milliliters of a liquid are needed to administer a given amount of a drug

and are most easily calculated by using a proportion after units are made consistent as follows:

$$\frac{\text{Original dose}}{\text{Per amount}} = \frac{\text{Desired dose}}{\text{Per amount}}$$

Some drugs are manufactured in units (U) rather than in grams or milligrams. Examples are penicillin, insulin, and heparin. Solving dose problems for these drugs is exactly the same as for the other dosage units previously mentioned.

Example 3

A brand of sodium heparin is available as 1000 U/mL. How many milliliters do you need for 500 U of the drug?

Solution: Utilizing (Original dose)/(Per amount) = (desired dose)/(per amount)

$$1000 \text{ U}/1 \text{ mL} = 500 \text{ U}/x \text{ mL}$$

Set up the proportion in the prepared-strength formula.
By cross-multiplying, we obtain:

$$1000(x) = 500$$

Divide both sides by 1000 to isolate x:

$$\frac{1000(x)}{1000} = \frac{500}{1000}$$

$$x \text{ mL} = 0.5 \text{ mL}$$

Answer

The amount required for 500 U, given the prepared-strength liquid, is 0.5 mL.

There is no universal equivalence between units as a measure of amount and the metric weight system. Units are used with biologic standardization and are defined for each drug by a standard preparation of that drug when the drug is measured in units. For example, there is a standard preparation of digitalis consisting of dried, powdered digitalis leaves; 100 mg of this preparation equals 1 United States Pharmacopeia (USP) unit of activity. In this way when drugs are extracted from animals, plants, or minerals, there is a standard reference preparation. Note that 100 mg is not 1 U for every drug with units; for example, insulin has a standard preparation of 0.04 mg = 1 U. When a drug is isolated as a pure chemical form, either extracted as the active substance in a natural source or synthesized in the laboratory, biologic standardization based on a standard preparation from the natural source is no longer necessary. The specific chemical amount is given in metric weight or volume measure.

Calculations With a Dosage Schedule

Sometimes the dose of a drug must be obtained from a **schedule**, which may be based on the size of a person. For example, a suggested schedule for albuterol syrup in children ages 2 to 6 years is 0.1 mg/kg of body weight. This means that the *dose* must be calculated after the body weight is obtained, and then the amount of the drug preparation needed for treatment can be calculated.

Example 4

Using a schedule of 0.1 mg/kg for albuterol syrup and a prepared-strength mixture of 2 mg/5 mL, how much of the syrup is needed for a 20-kg child?

Solution:

Calculate the dose needed:

$$\text{Dose} = 0.1 \text{ mg/kg} \times 20 \text{ kg} = 2.0 \text{ mg}$$

or

$$\frac{0.1 \text{ mg}}{1 \text{ kg}} = \frac{x}{20 \text{ kg}}$$

Next, calculate the amount of the preparation by cross-multiplying and solving for x:

$$\frac{2 \text{ mg}}{5 \text{ mL}} = \frac{2 \text{ mg}}{x \text{ mL}}$$

Simplifying,

$$2(x) = 10$$

$$x \text{ mL} = 5 \text{ mL}$$

Answer

This 20-kg child needs 5 mL of albuterol syrup.

Additional Examples: Prepared-Strength Drugs

Example 5

An injectable solution of glycopyrrolate with a prepared strength of 0.2 mg/mL is used for nebulization. How many milliliters are needed for a 1.5-mg dose?

Solution:

Original dose per amount: 0.2 mg/mL

Desired dose: 1.5 mg

Amount needed: x mL

Substituting:

$$\frac{0.2 \text{ mg}}{1 \text{ mL}} = \frac{1.5 \text{ mg}}{x \text{ mL}}$$

Using cross-multiplication to simplify:

$$0.2 \text{ mg}(x) = 1.5 \text{ mg}(1 \text{ mL})$$

$$x = \frac{1.5}{0.2}$$

$$x \text{ mL} = 7.5 \text{ mL}$$

Answer

An amount of 7.5 mL will contain the desired dose of 1.5 mg, using the prepared strength given.

Example 6

You have 1 mg/mL of terbutaline in an ampule for injection. How much do you need to give a 0.25-mg dose subcutaneously?

Solution:

Original dose per amount: 1 mg/mL

Desired dose: 0.25 mg

Amount needed: x mL

Substituting:

$$\frac{1 \text{ mg}}{1 \text{ mL}} = \frac{0.25 \text{ mg}}{x \text{ mL}}$$

Solving for x :

$$\begin{aligned} 1 \text{ mg} (x \text{ mL}) &= 0.25 \text{ mg} (1 \text{ mL}) \\ x &= 0.25 \text{ mL} \end{aligned}$$

Answer

Give 0.25 mL for the desired dose of 0.25 mg.

Example 7

A dosage schedule for a surfactant (see [Chapter 10](#)) calls for 5 mL/kg of body weight. If a premature infant weighs 1200 g, how many milliliters are needed?

Solution:

Convert body weight to kilograms:

$$1 \text{ kg}/1000 \text{ g} \times 1200 \text{ g} = 1.2 \text{ kg}$$

Multiply the weight in kilograms by the schedule of 5 mL/kg:

$$x \text{ mL} = 1.2 \text{ kg} \times 5 \text{ mL/kg} = 6 \text{ mL}$$

Answer

On the basis of the dosage schedule and weight, 6 mL should be given.

Example 8

The prepared strength of a drug is 100 mg/4 mL. The dosage schedule is 100 mg/kg of birth weight. A premature newborn weighs 1100 g. Based on the weight of the newborn, what dosage is needed? How many milliliters of the drug should be given to achieve this dose?

Solution: To determine the dose that is needed, perform two steps:
Convert the birth weight to kilograms:

$$1 \text{ kg}/1000 \text{ g} \times 1100 \text{ g} = 1.1 \text{ kg}$$

Multiply the birth weight by the dosage schedule to find the dose required:

$$x \text{ mg} = 100 \text{ mg/kg} \times 1.1 \text{ kg} = 110 \text{ mg}$$

The dose needed is 110 mg of drug.

Solution: To find the number of milliliters required to achieve this dose:

Original dose per amount: 100 mg/4 mL

Desired dose: 110 mg

Amount needed: x mL

Substituting:

$$\frac{100 \text{ mg}}{4 \text{ mL}} = \frac{110 \text{ mg}}{x \text{ mL}}$$

$$100 \text{ mg} (x) = 110 \text{ mg} (4 \text{ mL})$$

$$x = [110 \text{ mg} (4 \text{ mL})] / 100$$

$$x = 4.4 \text{ mL}$$

Answer

On the basis of the dosage schedule, the weight of the newborn, and the prepared strength, 4.4 mL will give the needed dose of 110 mg.

Calculating Doses From Percent-Strength Solutions

KEY POINT

Calculating doses based on a percent-strength concentration of a solution can be done by using the following equation:

$$\begin{aligned} &\text{Percent strength (in decimals)} \\ &= \frac{\text{Solute (in grams or cubic centimeters)}}{\text{Total amount (solute and solvent)}} \end{aligned}$$

Because an area of expertise for respiratory therapists is solutions for aerosolization, solutions and percent strengths often are needed to calculate a drug dose. A **solution** contains a **solute**, which is dissolved in a **solvent**, giving a homogeneous mixture. The **strength** of a solution is expressed as the percentage of solute relative to total solvent and solute. **Percent** means parts of the active ingredient (solute) in a preparation contained in 100 parts of the total preparation (solute *and* solvent).

Types of Percent Preparations

Weight to Weight

Percent weight to weight (W/W) expresses the number of grams of a drug or active ingredient in 100 g of a mixture:

$$\text{W/W: Grams per 100 g of mixture}$$

Weight to Volume

Percent weight to volume (W/V) may be expressed as the number of grams of a drug or active ingredient in 100 mL of a mixture:

$$\text{W/V: Grams per 100 mL of mixture}$$

Volume to Volume

Percent volume to volume (V/V) expresses the number of milliliters of drug or active ingredient in 100 mL of a mixture:

$$\text{V/V: Milliliters per 100 mL of mixture}$$

Solutions by Ratio

When diluting a medication for use in an aerosol or intermittent positive-pressure breathing (IPPB) treatment, a solute-to-solvent ratio is frequently given (e.g., epinephrine 1 : 100).

Ratio by Grams to Milliliters

In the preceding example, the following is indicated:

$$1 \text{ g per 200 mL of solution} = \frac{1 \text{ g}}{200 \text{ mL}} = 0.005 \times 100 = 0.5\%$$

(Multiplying by 100 is the same as moving the decimal *two* places to the *right*.)

This is the ratio indicated in traditional examples, such as epinephrine 1 : 100, which is a 1% strength solution:

$$\frac{1 \text{ g}}{100 \text{ mL}} = 0.01 \times 100 = 1\%$$

Ratio by Simple Parts

In the following part-to-part example, actual parts of medication to parts of solvent are indicated:

1:8 = 1 part to 8 parts, which is the same as $\frac{1}{4}$ cc to 2 cc

Part-to-part ratios do not indicate actual amounts or specific units, although usually a ratio of milliliters to milliliters is meant. It is assumed you know that $\frac{1}{4}$ or $\frac{1}{2}$ cc of an agent is given as the usual dose and not 1 cc. An order such as 1:8 is not precise—without further specifications—about the amount of a drug (e.g., whether 0.25 mL or 0.5 mL) to be given.

Solving Percent-Strength Solution Problems

For solutions in which the active ingredient itself is pure (undiluted, 100% strength), the following equation can be used:

Equation 1

$$\begin{aligned} &\text{Percent strength (in decimals)} \\ &= \frac{\text{Solute (in gram or cubic centimeters)}}{\text{Total amount (solute and solvent)}} \end{aligned}$$

Alternatively, a ratio format can be used:

Equation 2

$$\frac{\text{Amount of solute}}{\text{Total amount}} = \frac{\text{Amount of solute}}{100 \text{ parts (grams or cubic centimeters)}}$$

When the active ingredient, or solute, is already diluted and less than pure, the following equation can be used:

Equation 3

$$\begin{aligned} &\text{Percent strength (in decimals)} \\ &= \frac{(\text{Dilute solute}) \times (\text{Percent strength of solute})}{\text{Total amount (solution)}} \end{aligned}$$

In Eq. 3, the solute (active ingredient) multiplied by the percent strength gives the amount of pure active ingredient in the dilute solution. This equation adds only one modification to the formula given in Eq. 1—multiplying the dilute solute by its actual percent strength, with the result indicating the amount of active ingredient at a 100% (pure) strength. For example, 10 mL of 10% solute means you have 1 mL of pure (100%) solute. Put another way, you would need 10 mL of dilute solute to have 1 mL of

pure solute (active ingredient). When used in Eq. 3, the unknown is usually how much of the dilute solute, or active ingredient, is needed in the total solution to give the desired strength. The preceding equations are illustrated in the two examples below.

KEY POINT

Move the decimal point to convert easily between grams, percent strength, and milligrams per milliliter. If beginning with percent strength (e.g., 1%), move the decimal *one* place to the *right* to convert to milligrams per milliliter (e.g., 1% = 1.0% = 10 mg/mL). If beginning with percent strength (e.g., 10%), move the decimal *two* places to the *left* to convert to grams (e.g., 10% = 10.0% = 0.10 g).

Example 9

Undiluted active ingredient: How many milligrams of active ingredient are there in 2 cc of 1:200 isoproterenol?

Solution:

Percent strength: 1:200 = 0.5% = 0.005

Total amount of solution: 2 cc

Active ingredient: x

Substituting in Eq. 1:

$$0.005 = x \text{ g} / 2 \text{ cc}$$

$$x \text{ g} = 0.005 \times 2$$

$$x \text{ g} = 0.01 \text{ g or } 10 \text{ mg}$$

Answer

Converting 0.01 g to milligrams gives 10 mg. In 2 cc of 1:200 solution, there are 10 mg of isoproterenol.

Alternative Solution:

Percent strength : 1 : 200

$$\frac{1}{200} = 0.005 \text{ g}$$

Move the decimal point *two* places to the *right* (i.e., mathematically multiply by 100), and add a percent sign. At this point, the number changes from grams to a percent solution:

$$0.005 \text{ g} = 0.005 \times 100 = 0.5\%$$

or

$$0.005 \text{ g} = 0.005 \times 100 = 0.5\%$$

Move the decimal point an additional *one* place (for a total of *three* places, i.e., mathematically multiply by 1000) to convert from percent strength to milligrams per milliliter:

$$0.5\% = 5 = 5 \text{ mg/mL}$$

or

$$0.005 \text{ g} = 0.005 \times 1000 = 5 \text{ mg/mL}$$

The question asks how many milligrams of active ingredients are in 2 cc. If we remember that 1 cc = 1 mL and we know there are 5 mg in every 1 mL, we then multiply by 2 cc to obtain the answer: 10 mg/2 cc. (If you need to set up the equation, refer to the earlier section “Calculating With Proportions.”)

Example 10

Diluted active ingredient: How much 20% acetylcysteine is needed to prepare 5 cc of 10% acetylcysteine?

Solution: Using the equation for dilute active ingredients (here, the acetylcysteine is only of 20% strength, not pure), the following is obtained: Desired percent strength (in decimals): 10% = 0.10

Total amount of solution: 5 cc

Percent strength of solute (active ingredient): 20% = 0.20

Dilute solute (i.e., amount of active ingredient needed): x

Substituting in Eq. 3:

$$0.10 = x(0.20)/5 \text{ cc}$$

$$x = 5(0.10)/0.20$$

$$x = 2.5 \text{ cc of 20\% Mucomyst}$$

Answer

The 2.5 cc of 20% acetylcysteine is then mixed with 2.5 cc of normal saline to give a total of 5 cc of solution. This 5 cc will be a 10% strength solution.

Although diluting a 20% solution to a 10% solution is obviously a “half-and-half” procedure and does not require the use of an equation, less intuitive dilutions may need to be calculated. You might try diluting 20% acetylcysteine to obtain 5 cc of a 5% strength solution by using the preceding approach.

Alternative Solution: Convert 10% to 100 mg/mL by moving the decimal *one* place to the *right* (think of it as 10%, move one place, drop the percent sign, and add mg/mL, and it becomes 100 mg/mL; or change the percent to a decimal, and multiply by 1000 (10% = 0.10 $\times$ 1000 = 100 mg/mL). What the question really is asking is how many milligrams are in 5 cc of 10% acetylcysteine. That is easy: We already know there are 100 mg for every 1 cc of drug, so multiply 100 mg $\times$ 5 cc, equaling 500 mg. This is the desired dose, and the original dose is 20%, or 200 mg/mL. Set up the proportions equation (refer to the earlier section “Calculating With Proportions”):

Original dose per amount: 200 mg/1 mL

Desired dose: 500 mg

Amount desired: x mL

Substituting:

$$\frac{200 \text{ mg}}{1 \text{ mL}} = \frac{500 \text{ mg}}{x \text{ mL}}$$

Cross-multiply:

$$\frac{200 \text{ mg} (x \text{ mL})}{200 \text{ mg}} = \frac{500 \text{ mg} (1 \text{ mL})}{200 \text{ mg}}$$

$$x = 2.5 \text{ cc of 20\% Mucomyst}$$

Answer: The 2.5 cc of the 20% acetylcysteine is then mixed with 2.5 cc of normal saline to give a total solution volume of

5 cc. This 5 cc will be a 10% strength solution. The key is to know the amount of milligrams of drug that is ordered. There is no difference between 5 cc of 10% strength solution and 2.5 cc of 20% solution. They both equal what is ultimately desired—500 mg of the drug.

Summary

Calculations with solutions of drugs, using percent strengths, can be summarized into four important points:

1. Convert to metric units and decimal expressions.
2. Substitute known entities in the appropriate equation (undilute or dilute active ingredient).
3. Use grams or milliliters in the percent equation.
4. Express the answer in the units requested.

Quantity Sufficient

When mixing solutions, determine the amount of active ingredient needed for the percent strength desired and then add enough solvent to “top off” to the total solution amount needed. When ordering a solution, the total needed is indicated by *quantity sufficient* (qs). For example, to obtain 30 cc of 3% procaine hydrochloride (HCl), we calculate 0.9 cc of the active ingredient and add water qs for 30 cc of solution. Do not merely give the difference between solute and total solution (30 cc – 0.9 cc = 29.1 cc), because certain solutes can change volume (e.g., alcohol “shrinks” in water).

Percent Strengths in Milligrams per Milliliter

The basic definition of percent strength in solutions involves grams or milliliters. However, the amount of active ingredient in most nebulized drug solutions is in milligrams. A useful and easily remembered clinical reference is to define percent strengths in terms of milligrams per single milliliter by using a 1% strength reference point. Recall that 1% strength is 1 g/100 mL. Using Eq. 1 for percent strength, you have:

$$0.01 = \frac{1 \text{ g}}{100 \text{ mL}}$$

For 1 mL of a 1% strength solution, you would have:

$$0.01 = \frac{x \text{ g}}{1 \text{ mL}}$$

$$x \text{ g} = 0.01 \text{ g}$$

and $0.01 \text{ g} \times 1000 \text{ mg/g} = 10 \text{ mg}$.

Because 0.01 g equals 10 mg, you have 10 mg/mL in a 1% solution. The 1% strength is an easily learned reference point. Table 4.2 lists some common percent strengths, giving amounts in milligrams per milliliter, in reference to the 1% concentration.

Note the relationship of 1% to 10%: If there are 10 mg/mL in a 1% solution, there would be 10 times that amount in a 10% solution, or 100 mg/mL. Likewise, a 0.5% solution has one half as much active ingredient as a 1% solution—one half of 10 mg/mL would be 5 mg/mL. This amount of 5 mg/mL could have been used to solve Example 9, an undiluted active ingredient percentage problem. In Example 9, it was found that a 1 : 200 solution (a 0.5% strength solution) has 10 mg in 2 mL, which is the same as 5 mg in 1 mL.

TABLE 4.2 Drug Amounts in Milligrams per Milliliter for Common Percent Strengths

Percent Strength (%)	Drug Amount (mg/mL)
20	200
10	100
5	50
1	10
0.5	5
0.1	1
0.05	0.5

Note: Starting with percent strength, move the decimal *one* place to the *right*, and it becomes a drug amount.

KEY POINT

An easy reference point for the amount of drug contained in a solution, in milligrams per milliliter, is 1% strength, which is 10 mg/mL.

Eqs. 1 and 3 (see above) should be memorized; they represent a more general statement of percent strengths for solving any problem. However, knowledge of milligrams per milliliter for a 1% solution can be very helpful in many problems to know how many milligrams of the active ingredient are being given. Examples of drug solutions with the strengths listed in Table 4.2 can be given. Albuterol is available as a 0.5% solution or 5 mg/mL, and an ampule of terbutaline (1 mg/cc) is a 0.1% strength solution.

You can easily convert from gram to percent strength to milligrams per milliliter by simply moving the decimal point—no mathematical calculation is needed. Or, in a mathematical approach, multiply the amount of grams by 1000 to achieve milligrams ($0.001 \text{ g} \times 1000 = 1 \text{ mg}$). This math works for any drug expressed as grams, percent strength, or milligrams per milliliter. Using the preceding example:

$$0.001 \text{ g} = 0.1\% = 1 \text{ mg/mL}$$

Move the decimal point *two* places to the *right* to convert from grams to percent strength. From a percent-strength amount, move the decimal *one* place to the *right* to convert to milligrams per milliliter.

This process can be reversed:

$$50 \text{ mg/mL} = 5\% = 0.05 \text{ g}$$

If you begin with milligrams per milliliter, move the decimal point *one* place to the *left* to convert to percent strength. From a percent strength, move the decimal point *two* places to the *left* to convert to grams.

Diluents and Drug Doses

A persisting common misconception is that the amount of diluent added to a liquid drug to be aerosolized by nebulization is intended to “weaken” the dose or strength delivered to the patient. The amount of diluent affects the time required to nebulize a given solution but not the amount of active ingredient in

a nebulizer reservoir. Whether it is diluted with 2 cc or 10 cc of normal saline, $\frac{1}{2}$ cc of a 1% drug solution has the same amount (5 mg) of active ingredient. Practicality dictates that 2.5 cc of solution nebulizes in a reasonable time limit of 10 minutes or so, whereas 10 cc may take much longer. The diluent is also needed because disposable nebulizers cannot create an aerosol with less than approximately 1 mL of solution in the reservoir (the dead volume). Theoretically, given a suitable nebulizing device, there is no reason that the original 0.5 cc of 1% drug could not be nebulized undiluted to deliver the dose of 5 mg. The amount of the active ingredient, determined by the percent strength and quantity in cubic centimeters of the drug, gives a dose amount. Although technically the percent strength of the resulting solution in the reservoir is weaker, the dose remains unchanged at 5 mg. It is the dose in milligrams that should be of significance to the clinician.

Additional Examples: Solutions**Example 11**

How many milligrams of active ingredient are in 3 cc of a 2% solution of procaine HCl?

Solution: Use the percentage formula of Eq. 1 for a pure-strength ingredient:

$$\text{Percent strength (in decimals)} = \frac{\text{Solute}}{\text{Total amount}}$$

Convert the percentage to decimals and substitute the known values:

$$0.02 = \frac{x \text{ g}}{3 \text{ cc}}$$

$$0.02 (3 \text{ cc}) = x \text{ g}$$

$$x \text{ g} = 0.06 \text{ g}$$

In milligrams:

$$0.06 \text{ g} \times 1000 \text{ mg/g} = 60 \text{ mg}$$

Answer

In 3 cc of a 2% solution of procaine HCl, there is 60 mg of active ingredient.

Alternative Solution: Moving the decimal can easily convert to milligrams per milliliter. If we think of 2% as 2.0% and move the decimal *one* place to the *right*, we convert the percent to 20 mg/mL. Remember that 1 mL equals 1 cc, so if we need to find how many milligrams of active ingredient are in 3 cc of solution, we simply multiply 3 cc by 20 mg/mL to equal 60 mg. The reader can use the proportions equation to confirm:

$$\frac{20 \text{ mg}}{1 \text{ mL}} = \frac{x}{3 \text{ cc}}$$

Cross-multiply and solve for x :

$$\begin{aligned} x(1 \text{ mL}) &= 20 \text{ mg} (3 \text{ cc}) \\ x &= 60 \text{ mg} \end{aligned}$$

Example 12

A resident wants to dilute 20% acetylcysteine to a strength of 6% for a research study. How many milliliters of 20% drug solution are needed to have 10 mL of 6% strength?

Solution: Use the modified Eq. 3 for calculating the dilute active ingredient:

$$\begin{aligned} &\text{Percent strength (decimals)} \\ &= \frac{(\text{Dilute solution}) \times (\text{Percent strength of solute})}{\text{Total amount (solution)}} \end{aligned}$$

Percent strength desired: 6% = 0.06

Dilute solute: unknown = x mL

Percent strength: 20% = 0.20

Total amount of solution: 10 mL

Substituting and solving:

$$\begin{aligned} 0.06 &= \frac{(x \text{ mL}) \times 0.20}{10 \text{ mL}} \\ 0.06(10 \text{ mL}) &= x \text{ mL} (0.20) \\ x &= 0.06(10) / 0.20 \\ x \text{ mL} &= 3 \text{ mL} \end{aligned}$$

Answer

Draw up 3 mL of the 20% strength and add saline qs for a total of 10 mL. Check your calculation for correctness: 3 mL of 20% strength solution has 600 mg of active ingredient (20% = 200 mg/mL), 600 mg is 0.6 g, and 0.6 g/10 mL (or 6 g/100 mL) is a 6% strength. You obtained the needed amount of drug with 3 mL of the 20% solution.

Alternative Solution: First, we convert the needed amount of drug. The resident asks for 10 mL at 6% strength, so we convert 6% to 60 mg/mL by moving the decimal *one* place to the *right*. If we need 10 mL, then we multiply 10 mL $\times$ 60 mg, which equals 600 mg. We now know the resident needs 600 mg of drug. How do we know how much of the 20% strength is needed? We convert 20% to 200 mg/mL and set up the equation as a proportion (original dose/per amount = desired dose/per amount):

$$\frac{200 \text{ mg}}{1 \text{ mL}} = \frac{600 \text{ mg}}{x}$$

Cross-multiply and solve for x :

$$\begin{aligned} \frac{200 \text{ mg} (x)}{200 \text{ mg}} &= \frac{600 \text{ mg} (1 \text{ mL})}{200 \text{ mg}} \\ x &= 3 \text{ mL} \end{aligned}$$

Example 13

The usual dose of albuterol sulfate is 0.5 mL of a 0.5% strength solution. How many milligrams is this?

Solution: Using Eq. 1 for percent strength:

Percentage in decimals: 0.5% = 0.005

Active ingredient: unknown (x)

Total solution: 0.5 mL

Substituting:

$$0.005 = \frac{x \text{ g}}{0.5 \text{ mL}}$$

$$x = 0.005(0.5) = 0.0025 \text{ g}$$

Converting:

$$0.0025 \text{ g} = 2.5 \text{ mg}$$

Answer

There is 2.5 mg of active ingredient in the usual dose.

Alternative Solution: First we need to convert the percent solution to milligrams per milliliter. To do this, move the decimal *one* place to the *right* to convert to milligrams per milliliter (0.5% = 5 mg/mL). If we know that there are 5 mg in 1 mL and we need 0.5 mL, all we need to do is halve 5 mg, which is 2.5 mg.

Example 14

Albuterol sulfate is also available as a unit dose of 3 mL at a percent strength of 0.083%. If the entire amount of 3 mL is given, is this the same as the usual dose of 2.5 mg?

Solution: Using Eq. 1 for percent strength:

Percent strength (in decimals): 0.083% = 0.00083

Active ingredient: unknown = x

Total amount of solution: 3 mL

Substituting:

$$0.00083 = \frac{x \text{ g}}{3 \text{ mL}}$$

$$x \text{ g} = 3(0.00083) = 0.00249 \text{ g}$$

$$\text{and } 0.00249 \text{ g} = 2.49 \text{ mg}$$

Answer

The result is approximately 2.5 mg, the usual dose.

Alternative Solution: First, we need to convert 0.083% to milligrams per milliliter. To do this, we move the decimal *one* place to the *right* to convert to milligrams per milliliter (0.083% = 0.83 mg/mL). Set up the proportions equation and solve for x :

$$\frac{0.83 \text{ mg}}{1 \text{ mL}} = \frac{x}{3 \text{ mL}}$$

$$0.83(3) = x$$

$$2.49 = x$$

Rounding up, we obtain 2.5 mg.

Example 15

Terbutaline sulfate is available as 1 mg per 1 mL of solution. What percent strength is this?

Solution: Convert 1 mg to 0.001 g ($1 \text{ mg} \times 1 \text{ g}/1000 \text{ mg} = 0.001 \text{ g}$). Then,

$$x = \frac{0.001 \text{ g}}{1 \text{ mL}}$$

$$x = 0.001 = 0.1\%$$

Answer

The percent strength is 0.1%.

Alternative Solution: This is straightforward; all we need to do is remember to move the decimal *one* place to the *left*. This will convert to percent strength ($1 \text{ mg/mL} = 0.1\%$).

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

Prepared-Strength Dose Calculations

1. A bottle is labeled Demerol (meperidine) 50 mg/cc. How many cubic centimeters are needed to give a 125-mg dose?
2. An agent comes as 500 mg/10 mL. How many milliliters are needed to give a 150-mg dose?
3. Hyaluronidase comes as 150 U/cc. How many cubic centimeters are needed for a 30-U dose?
4. Morphine sulfate 4 mg is ordered; you have a vial with 10 mg/mL. How much do you need?
5. A dosage schedule for the surfactant poractant alfa calls for an infant with a 2.5 mL/kg birth weight. How much of the drug will you need for an infant weighing 800 g?
6. Diphenhydramine (Benadryl) elixir contains 12.5 mg of diphenhydramine HCl in each 5 mL of elixir. How many milligrams are there in a $\frac{1}{2}$ teaspoonful dose (1 tsp = 5 mL)?
7. A pediatric dose of 100 mg of a syrup is ordered. The dosage form is an oral suspension containing 125 mg/5 cc. How much of the suspension contains a 100-mg dose?
8. How many units of heparin are found in 0.2 mL, if you have 1000 U/mL?
9. Albuterol syrup is available as 2 mg/5 mL. If a dosage schedule of 0.1 mg/kg is used, how much syrup is needed for a 30-kg child? How many teaspoons is this?
10. Terbutaline is available as 2.5-mg tablets. How many tablets do you need for a 5-mg dose?
11. If a cough syrup is available as 120 mg/5 mL, how much of the drug is there in $\frac{1}{2}$ tsp?
12. Theophylline is available as 250 mg/10 mL and is given intravenously at 6 mg/kg body weight. How much solution do you give to a 60-kg woman?
13. Terbutaline sulfate is available as 1 mg/mL in an ampule. How many milliliters are needed for a 0.25-mg dose?
14. A patient is told to take 4 mg of albuterol four times daily. The medication comes in 2-mg tablets. How many tablets are needed for one 4-mg dose?
15. An agent is available as a syrup with 10 mg/5 mL. How many teaspoons should be taken for a 20-mg dose?
16. If an agent is available at 3 mg/mL, how many milliliters are needed for a dose of 9 mg?
17. If a dosage schedule requires 0.25 mg/kg of body weight, what dosage is needed for an 88-kg person?
18. If theophylline is available as 80 mg/15 mL, how much is needed for a 100-mg dose?
19. How much of a drug is needed for a 65-kg adult, using 0.5 mg/kg?

20. The pediatric dosage of an antibiotic is based on 0.5-g/20-lb body weight, not to exceed 75 mg/kg/24 hr.
 - a. What is the dose for a 40-lb child?
 - b. If this dose is given twice in 1 day, has the maximal dose been exceeded?

Percent-Strength Solutions

1. How many grams of calamine are needed to prepare 120 g of an ointment containing 8% calamine?
2. In 147 mL of solution, there is 1 mL of active enzyme. What is the percent strength of active enzyme in the solution?
3. If theophylline is available in a 250-mg/10-mL solution, what percent strength is this?
4. You have epinephrine 1:100. How many milliliters of epinephrine would be needed to contain 30 mg of active ingredient?
5. A dose of 0.4 mL of epinephrine HCl 1:100 is ordered. This dose contains how many milligrams of epinephrine HCl (the active ingredient)?
6. If you administer 3 mL of a 0.1% strength solution, how many milligrams of active ingredient have you given?
7. A drug is available as a 1:200 solution and the maximal dose that may be given by aerosol for a particular patient is 3 mg. What is the maximal amount of solution (in milliliters) that may be used?
8. Epinephrine 1:1000 contains how many milligrams of active ingredient per milliliter?
9. How many milligrams per milliliter are there in 0.3 mL of a 5% strength agent?
10. How many milligrams of sodium chloride are needed for 10 mL of a 0.9% solution?
11. If you have lidocaine (Xylocaine) at 5 mg/mL, what percent strength is it?
12. A 0.5% strength solution contains how many milligrams in 1 mL?
13. Cromolyn sodium contains 20 mg in 2 mL of water. What is the percent strength?
14. How much active ingredient of acetylcysteine have you given with 4 cc of a 20% solution?
15. You have 20% acetylcysteine; how many milliliters of this do you need to form 4 mL of an 8% solution?
16. The recommended dose of an agent with a percent strength of 5% is 0.3 cc. How many milligrams of solute are there in this amount?
17. Acetylcysteine was marketed as 10% acetylcysteine with 0.05% isoproterenol. How many milligrams of each ingredient were in a 4-cc dose of solution? (Isoproterenol: $0.0005 = x \text{ g}/4 \text{ cc}$; $x = 0.002 \text{ g} = 2 \text{ mg}$.)
18. Which contains more drug: $\frac{1}{2}$ cc of a 1% drug solution with 2 mL of saline or $\frac{1}{2}$ cc of a 1% drug solution with 5 mL of saline?
19. How many milligrams per milliliter are in a 20% solution?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A pediatric resident is treating a child with croup and orders 5.625 mg of racemic epinephrine aerosolized. How many milliliters of racemic epinephrine will you dispense to the patient?

Reference

1. Chatburn, R. L. (1988). Measurement, physical quantities, and le Système International d'Unités (SI units). *Respiratory Care*, 33, 861.

5

Central and Peripheral Nervous Systems

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Nervous System

Autonomic Branches

- Parasympathetic and Sympathetic Regulation
- Neurotransmitters
- Efferent and Afferent Nerve Fibers
- Terminology of Drugs Affecting the Nervous System

Parasympathetic Branch

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- Nonadrenergic, Noncholinergic Inhibitory Nerves
- Nonadrenergic, Noncholinergic Excitatory Nerves

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms pertaining to the central and peripheral nervous systems
2. Classify the branches of the nervous system
3. Differentiate among the *central, peripheral, and autonomic nervous systems*
4. Discuss the use of *neurotransmitters*
5. Explain in detail the difference between the *parasympathetic* and *sympathetic* branches of the nervous system
6. Differentiate between the effects of *cholinergic* and *anticholinergic agents* on the nervous system
7. Differentiate between the effects of *adrenergic* and *antiadrenergic agents* on the nervous system
8. Discuss the various receptors in the airways
9. Differentiate among *nonadrenergic, noncholinergic inhibitory, and excitatory* nerves

KEY TERMS AND DEFINITIONS

Acetylcholine (ACh) Chemical produced by the body that is used in the transmission of nerve impulses. It is destroyed by the enzyme cholinesterase.

Adrenergic (adrenomimetic) Refers to a drug stimulating a receptor for norepinephrine or epinephrine.

Afferent Signals that are transmitted to the brain and spinal cord.

Antiadrenergic Refers to a drug blocking a receptor for norepinephrine or epinephrine.

Anticholinergic Refers to a drug blocking a receptor for acetylcholine.

Central nervous system (CNS) System that includes the brain and spinal cord; controls voluntary and involuntary acts.

Cholinergic (cholinomimetic) Refers to a drug causing stimulation of a receptor for acetylcholine.

Efferent Signals that are transmitted from the brain and the spinal cord.

Norepinephrine Naturally occurring catecholamine produced by the adrenal medulla that has properties similar to those of epinephrine. It is used as a neurotransmitter in most sympathetic terminal nerve sites.

Parasympatholytic Agent blocking or inhibiting the effects of the parasympathetic nervous system.

Parasympathomimetic Agent causing stimulation of the parasympathetic nervous system.

Peripheral nervous system (PNS) Portion of the nervous system outside the CNS, including sensory, sympathetic, and parasympathetic nerves.

Sympatholytic Agent blocking or inhibiting the effect of the sympathetic nervous system.

Sympathomimetic Agent causing stimulation of the sympathetic nervous system.

The goal of this chapter is to provide a clear introduction to and understanding of the peripheral nervous system, its control mechanisms—especially neurotransmitter functions—and its physiologic effects in the body. Understanding of the control mechanisms and physiologic effects forms the basis for a subsequent understanding of drug actions and drug effects, both for agonists and for antagonists that act at various points in the nervous system. This chapter concludes with a summary of autonomic and other neural control mechanisms and their effects in the pulmonary system.

Nervous System

KEY POINT

One of the major control systems in the body is the *nervous system*, comprising *sensory* afferent nerves; *motor* efferent nerves; and the *autonomic nervous system*, which is divided further into the *sympathetic* and *parasympathetic* branches.

There are two major control systems in the body: the *nervous system* and the *endocrine system*. Both systems of control can be manipulated by drug therapy, which either mimics or blocks the usual action of the control system to produce or inhibit physiologic effects. The endocrine system is considered separately in [Chapter 11](#), which discusses the corticosteroid class of drugs. The nervous system is divided into the **central nervous system (CNS)** and the **peripheral nervous system (PNS)**, both of which offer sites for drug action. The overall organization of the nervous system may be outlined as follows:

- I. Central nervous system
 - A. Brain
 - B. Spinal cord
- II. Peripheral nervous system
 - A. Sensory (afferent) neurons
 - B. Somatic (motor) neurons
 - C. Autonomic nervous system
 1. Parasympathetic branch
 2. Sympathetic branch

[Fig. 5.1](#) is a functional, but not anatomically accurate, diagram of the CNS and the PNS. The *sensory* branch of the nervous system consists of afferent neurons from heat, light, pressure, and pain receptors sending information from the periphery to the CNS. The *somatic* portion (or motor branch) of the nervous system is under voluntary, conscious control and innervates skeletal muscle

for motor actions, such as lifting, walking, or breathing. This portion of the nervous system is manipulated by neuromuscular blocking agents that induce paralysis in surgical procedures or during mechanical ventilation. The *autonomic nervous system* is the involuntary, unconscious control mechanism of the body, sometimes said to control vegetative or visceral functions. For example, the autonomic nervous system regulates heart rate; pupillary dilation and contraction; glandular secretion, such as salivation; and smooth muscle contraction in blood vessels and the airway. The autonomic nervous system is divided into the *parasympathetic* and *sympathetic* branches.

Autonomic Branches

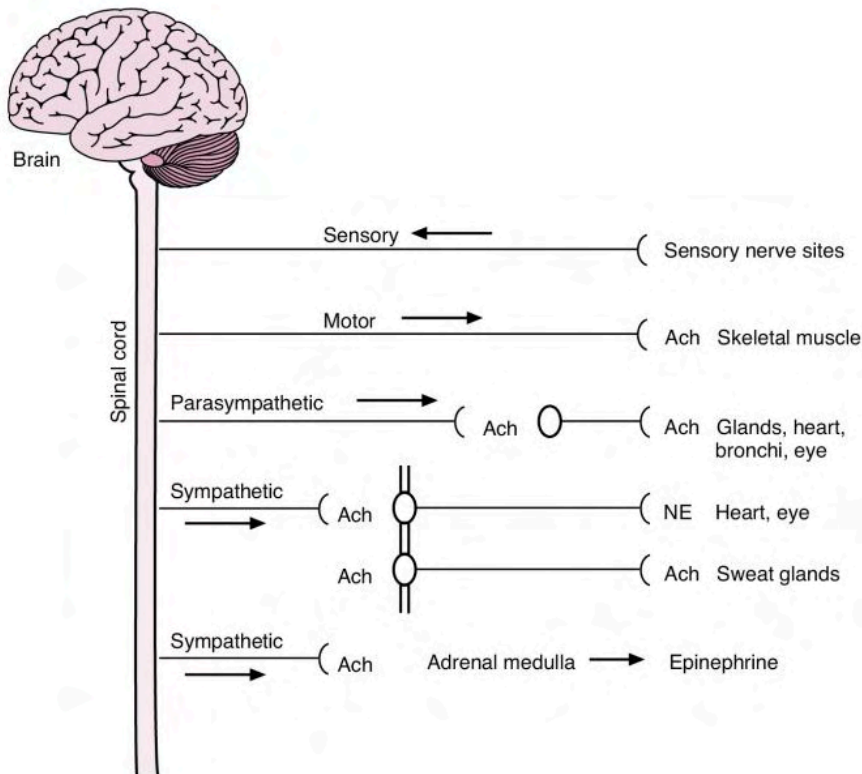
Neither motor nor sensory branch neurons have synapses outside the spinal cord before reaching the muscle or sensory receptor site. The motor neuron extends without interruption from the CNS to the skeletal muscle, and its action is mediated by the neurotransmitter **acetylcholine (ACh)**. This is in contrast to the synapses occurring in the sympathetic and parasympathetic divisions of the autonomic system. The multiple synapses of the autonomic system offer potential sites for drug action, as do the terminal neuroeffector sites.

The parasympathetic branch arises from the craniosacral portions of the spinal cord and consists of two types of neurons—a preganglionic fiber leading from the vertebrae to the ganglionic synapse outside the cord and a postganglionic fiber leading from the ganglionic synapse to the gland or smooth muscle being innervated. The parasympathetic branch has good specificity, with the postganglionic fiber arising very near the effector site (e.g., a gland or smooth muscle). As a result, stimulation of a parasympathetic preganglionic neuron causes activity limited to individual effector sites, such as the heart or the eye. [Fig. 5.2](#) illustrates the portions of the spinal cord where the parasympathetic and sympathetic nerve fibers originate.

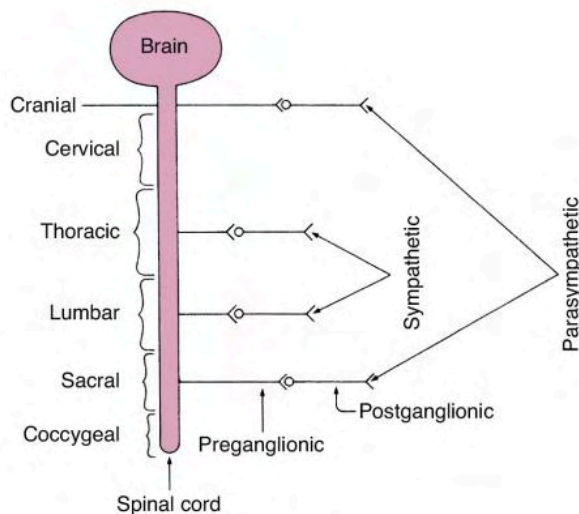
KEY POINT

Nerve impulses are conducted by electrical and chemical means; the chemical portion of nerve transmission is referred to as a *neurotransmitter*. The neurotransmitter is *acetylcholine (ACh)* at the *myoneural (neuromuscular) junction*, at the *ganglia*, and at the *parasympathetic end sites*. The neurotransmitter at *sympathetic end sites* is generally *norepinephrine*, except at sweat glands and the adrenal medulla, where *ACh* is the neurotransmitter.

The sympathetic branch arises from the thoracolumbar portion of the spinal cord and consists of short preganglionic fibers and long



• **Fig. 5.1** Functional diagram of central and peripheral nervous systems, indicating the somatic branches (sensory, motor) and the autonomic branches (sympathetic, parasympathetic), with their neurotransmitters. Ach, Acetylcholine; NE, norepinephrine.



• **Fig. 5.2** Parasympathetic nerve fibers arise from the cranial and sacral portions of the spinal cord, whereas sympathetic fibers leave the cord primarily from the thoracic and lumbar regions.

postganglionic fibers. Sympathetic neurons from the spinal cord terminate in ganglia that lie on either side of the vertebral column. In the *ganglia*, or the *ganglionic chain*, the preganglionic fiber makes contact with postganglionic neurons. As a result, when one sympathetic preganglionic neuron is stimulated, the action passes to many or all of the postganglionic fibers. The effect of sympathetic activation is widened further because sympathetic fibers innervate the adrenal medulla and cause the release of epinephrine

into the general circulation. Circulating epinephrine stimulates all receptors responding to **norepinephrine**, even if no sympathetic nerves are present. The parasympathetic system allows discrete control, whereas the design of the sympathetic system causes a widespread reaction in the body.

Parasympathetic and Sympathetic Regulation

There are general differences between the parasympathetic and sympathetic branches of the autonomic nervous system. Parasympathetic control is essential to life and is considered a more discrete, finely regulated system compared with sympathetic control. Parasympathetic effects control the day-to-day body functions, such as digestion, bladder and rectal discharge, and basal secretion of bronchial mucus. Overstimulation of the parasympathetic branch would render the body incapable of violent action, resulting in what is termed the *SLUD syndrome*: salivation, lacrimation, urination, and defecation. These reactions are definitely counterproductive to fleeing or fighting!

By contrast, the sympathetic branch reacts as a general alarm system and does not exercise discrete controls. This is sometimes characterized as a “fight or flight” system: heart rate and blood pressure increase, blood flow shifts from the periphery to the muscles and the heart, blood sugar increases, and the bronchi dilate. The organism prepares for maximal physical exertion. The sympathetic branch is not essential to life; animal models with sympathectomy can survive but are unable to cope with violent stress.

KEY POINT

Sympathetic effects are widespread, mediated by norepinephrine at nerve endings and by circulating epinephrine released from the adrenal medulla.

Neurotransmitters

Another general feature of the autonomic nervous system, including the sympathetic and parasympathetic branches, is the mechanism of neurotransmitter control of nerve impulses. Nerve impulse propagation is electrical and chemical (electrochemical). A nerve impulse signal is carried along a nerve fiber by *electrical* action potentials caused by ion exchanges (i.e., sodium [Na⁺] and potassium [K⁺]). At gaps in the nerve fiber between neurons (synapses), the electrical transmission is replaced by a chemical neurotransmitter. This is the *chemical* transmission of the electrical impulse, which occurs at the ganglionic synapses and at the end of the nerve fiber, termed the *neuroeffector site*. Identification of the chemical transmitters dates back to Loewi's experiments in 1921 and is fundamental to understanding autonomic drugs and their classifications. The usual neurotransmitters in the PNS, including the ganglionic synapses and terminal sites in the autonomic branches, are shown in Fig. 5.1 (Ach and norepinephrine).

Ach is the neurotransmitter conducting the nerve impulse at skeletal muscle sites; this site is referred to as the *neuromuscular junction* or the myoneural junction. In the parasympathetic branch, Ach is also the neurotransmitter at both the ganglionic synapse and the terminal nerve site, which is referred to as the *neuroeffector site*. In the sympathetic branch, Ach is the neurotransmitter at the ganglionic synapse; however, norepinephrine is the neurotransmitter at the sympathetic neuroeffector site. There are two exceptions to this pattern, both in the sympathetic branch. Sympathetic fibers to sweat glands release Ach instead of norepinephrine, and preganglionic sympathetic fibers directly innervate the adrenal medulla, where the neurotransmitter is Ach. Sympathetic fibers that have Ach at the neuroeffector sites are *cholinergic* (for Ach) sympathetic fibers.

"Cholinergic sympathetic" would be an apparent contradiction in terms if not for the exceptions to the rule—that is, norepinephrine being the sympathetic neurotransmitter. For example, sweating can be caused by giving a cholinergic drug, such as pilocarpine, although this effect is under sympathetic control. "Breaking out in a sweat," sweaty palms, and increased heart rate resulting from circulating epinephrine are common effects of stress or fright mediated by sympathetic discharge.

Although it is an oversimplification, an easy way to learn the various neurotransmitters initially is to remember that Ach is the neurotransmitter *everywhere* (skeletal muscle, all ganglionic synapses, and parasympathetic terminal nerve sites) *except* at the sympathetic terminal nerve sites, where norepinephrine is the neurotransmitter. The exceptions provided by sympathetic fibers releasing Ach can be remembered as exceptions to the general rule.

Efferent and Afferent Nerve Fibers

KEY POINT

The neurotransmitter Ach is terminated by the enzyme *cholinesterase*, and norepinephrine and sympathetic transmission are terminated by neurotransmitter *reuptake* into the *presynaptic neuron* (*uptake-1*) and by the enzymes *catechol O-methyltransferase (COMT)* and *monoamine oxidase (MAO)*.

The autonomic system is generally considered an **efferent** system—that is, impulses in the sympathetic and parasympathetic branches travel *from* the brain and spinal cord out *to* the various

neuroeffector sites, such as the heart, gastrointestinal tract, and lungs. **Afferent** nerves run alongside the sympathetic and parasympathetic efferent fibers and carry impulses *from* the periphery *to* the cord. The afferent fibers convey impulses resulting from visceral stimuli and can form a reflex arc of stimulus input–autonomic output, analogous to the well-known somatic reflex arcs, such as the knee-jerk reflex. The mechanism of a vagal reflex arc mediating bronchoconstriction is discussed further in Chapter 7, in conjunction with drugs used to block the parasympathetic impulses.

Terminology of Drugs Affecting the Nervous System

KEY POINT

The terms *cholinergic (cholinoceptor)* and *adrenergic (adrenoceptor)* are used for Ach and norepinephrine/epinephrine receptors in the two autonomic branches.

Terminology of drugs and drug effects on the nervous system can be confusing and may seem inconsistent. The confusion is caused by the fact that drugs and drug effects are derived from the type of nerve fiber (parasympathetic or sympathetic) or, alternatively, the type of neurotransmitter and receptor (Ach or norepinephrine). The following terms are based on the anatomy of the nerve fibers, to describe stimulation or inhibition:

Parasympathomimetic
Parasympatholytic
Sympathomimetic
Sympatholytic

Additional terms are used, according to the type of neurotransmitter and receptor. *Cholinergic* refers to Ach, and *adrenergic* is derived from *adrenaline*, another term for epinephrine, which is similar to norepinephrine and can stimulate sympathetic neuroeffector sites. Because Ach is the neurotransmitter at more sites than just parasympathetic sites and because receptors exist on smooth muscle or blood cells without any nerve fibers innervating them, these terms denote a wider range of sites than the anatomically based terms, such as *parasympathomimetic*.

Cholinergic can refer to a drug effect at a ganglion, a parasympathetic nerve ending site, or the neuromuscular junction. *Adrenergic* describes receptors on bronchial smooth muscle or on blood cells, where there are no sympathetic nerves. For this reason, *cholinergic* and *adrenergic* are not strictly synonymous with *parasympathetic* and *sympathetic*. **Cholinergic (cholinomimetic)** refers to a drug causing stimulation of a receptor for Ach. **Anticholinergic** refers to a drug blocking a receptor for Ach. **Adrenergic (adrenomimetic)** refers to a drug stimulating a receptor for norepinephrine or epinephrine. **Antiadrenergic** refers to a drug blocking a receptor for norepinephrine or epinephrine. *Cholinoceptor* is an alternative term for cholinergic receptor, and *adrenoceptor* is an alternative term for adrenergic receptor.

KEY POINT

Parasympathomimetic = Cholinergic
Parasympatholytic = Anticholinergic
Sympathomimetic = Adrenergic
Sympatholytic = Antiadrenergic

Parasympathetic Branch

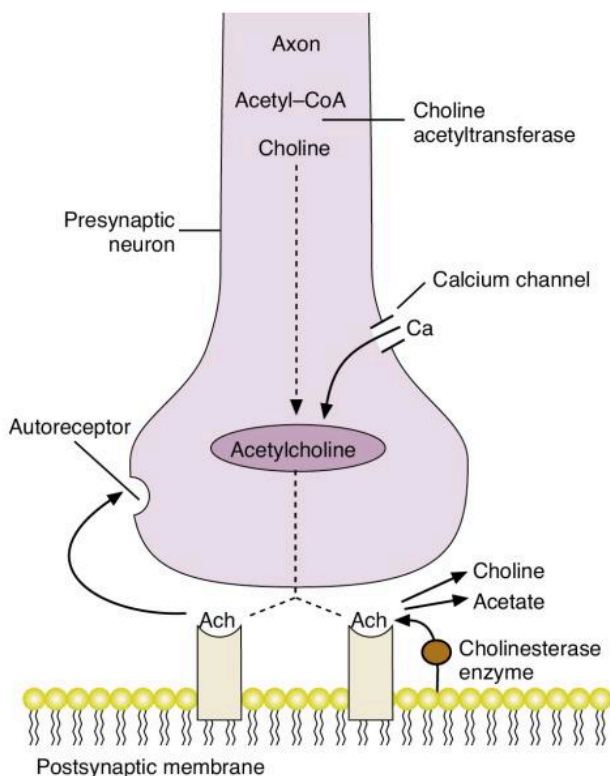
Cholinergic Neurotransmitter Function

KEY POINT

Parasympathetic effects on the cardiopulmonary system include decreased heart rate, lower blood pressure, bronchoconstriction, and mucus secretion in the airways.

In the parasympathetic branch, the neurotransmitter Ach conducts nerve transmission at the ganglionic site and at the parasympathetic effector site at the end of the postganglionic fiber. This action is illustrated in Fig. 5.3. The term *neurohormone* has also been used in place of *neurotransmitter*. Ach is concentrated in the presynaptic neuron (both at the ganglion and at the effector site). Ach is synthesized from acetyl-coenzyme A (CoA) and choline and catalyzed by the enzyme choline acetyltransferase. Ach is stored in vesicles in quantities of 1000 to 50,000 molecules per vesicle. When a nerve impulse (*action potential*) reaches the presynaptic neuron site, an influx of calcium is triggered into the neuron. Increased calcium in the neuron causes cellular secretion of the Ach-containing vesicles from the end of the nerve fiber. After release, Ach attaches to receptors on the postsynaptic membrane and initiates an effect in the tissue or organ site.

Ach is inactivated through hydrolysis by cholinesterase enzymes, which split the Ach molecule into choline and acetate, terminating stimulation of the postsynaptic membrane. In effect, the nerve impulse is “shut off.” There are also receptors on the



• **Fig. 5.3** Cholinergic nerve transmission mediated by the neurotransmitter acetylcholine (ACh). The action of the neurotransmitter is terminated by cholinesterase enzymes; attachment of acetylcholine to presynaptic autoreceptors inhibits further neurotransmitter release. CoA, Coenzyme A, used in synthesis; Ca, calcium ion.

presynaptic neuron, termed *autoreceptors*, which can be stimulated by Ach to regulate and inhibit further neurotransmitter release from the neuron. The effects of the parasympathetic branch of the autonomic system on various organs are listed in Table 5.1. Drugs can mimic or block the action of Ach to stimulate parasympathetic

TABLE 5.1 Effects of Parasympathetic Stimulation on Selected Organs or Sites

Organ/Site	Parasympathetic (Cholinergic) Response
Heart	
SA node	Slowing of rate
Contractility	Decreased atrial force
Conduction velocity	Decreased AV node conduction
Bronchi	
Smooth muscle	Constriction
Mucous glands	Increased secretion
Vascular Smooth Muscle	
Skin and mucosa	No innervation*
Pulmonary	No innervation*
Skeletal muscle	No innervation†
Coronary	No innervation*
Salivary Glands	
Increased secretion	
Skeletal Muscle	
None	
Eye	
Iris radial muscle	None
Iris circular muscle	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Gastrointestinal Tract	
Increased motility	
Gastrointestinal Sphincters	
Relaxation	
Urinary Bladder	
Detrusor	Contraction
Trigone sphincter	Relaxation
Glycogenolysis	
Skeletal muscle	None
Sweat Glands	
None†	
Lipolysis (Multiple Sites)	
None	
Renin Secretion (Kidney)	
None	
Insulin Secretion (Pancreas)	
Increased	

*No direct parasympathetic nerve innervation; response to exogenous cholinergic agonists is dilation.

†Dilation occurs as a result of sympathetic cholinergic discharge or as a response to exogenous cholinergic agonists.

‡Sweat glands are under sympathetic control; receptors are cholinergic, however, and the response to exogenous cholinergic agonists is increased secretion.

AV, Atrioventricular; SA, sinoatrial.

nerve ending sites (parasympathomimetics) or to block the transmission of such impulses (parasympatholytics). Both categories of drugs affecting the parasympathetic branch are commonly seen clinically. The effects of the parasympathetic system on the heart, bronchial smooth muscle, and exocrine glands should be mentally reviewed before considering parasympathetic agonists or antagonists (blockers):

- *Heart*: Slows rate (vagus)
- *Bronchial smooth muscle*: Constriction
- *Exocrine glands*: Increased secretion

Muscarinic and Nicotinic Receptors and Effects

Two additional terms are used to refer to stimulation of receptor sites for Ach. They are derived from the action in the body of two substances: the alkaloids *muscarine* and *nicotine*. Receptor sites that are stimulated by these two chemicals are illustrated in Fig. 5.4.

Muscarinic Effects

KEY POINT

Muscarinic (M) refers to cholinergic receptors at parasympathetic end sites. Muscarinic receptors are distinguished into subtypes M_1 through M_5 ; M_2 receptors are in the heart and M_3 receptors are on airway smooth muscle, mediating bronchoconstriction.

Muscarine, a natural product from the mushroom *Amanita muscaria*, stimulates Ach (cholinergic) receptors at the parasympathetic terminal sites: exocrine glands (lacrimal, salivary, and bronchial mucous glands), cardiac muscle, and smooth muscle (gastrointestinal tract). Ach receptors at these sites and the effects of parasympathetic stimulation at these sites are termed *muscarinic*. A muscarinic effect well known to respiratory care clinicians is the increase in airway secretions after administration of Ach-like drugs, such as neostigmine. A decrease in blood pressure is also caused by slowing of the heart and vasodilation. *In general, a parasympathomimetic effect is the same as a muscarinic effect, and a parasympatholytic effect is referred to as an antimuscarinic effect.*

Nicotinic Effects

KEY POINT

The term *nicotinic* refers to cholinergic receptors on ganglia and at the neuromuscular junction.

Nicotine, a substance in tobacco products, stimulates Ach (cholinergic) receptors at autonomic ganglia (parasympathetic and sympathetic) and at the skeletal muscle sites. Ach receptors at the autonomic ganglia and at the skeletal muscle are termed *nicotinic*, as are the effects on these sites of stimulation. Practical effects of stimulating these nicotinic receptors include an increase in blood pressure resulting from stimulation of sympathetic ganglia, causing vasoconstriction when the postganglionic fibers discharge, and muscle tremor caused by skeletal tissue stimulation.

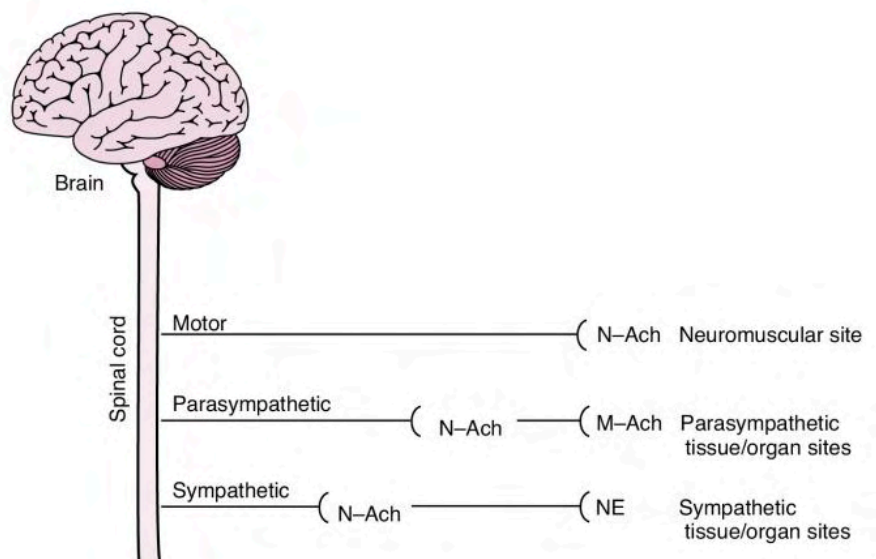
Subtypes of Muscarinic Receptors

Parasympathetic receptors and cholinergic receptors in general, with or without corresponding nerve fibers, are classified further into subtypes. These differences among cholinergic or muscarinic (M) receptors are based on different responses to different drugs, or recognition through use of DNA probes. Five muscarinic receptor subtypes have been identified: M_1 , M_2 , M_3 , M_4 , and M_5 . They are all G protein-linked (see Chapter 2). As G protein-linked receptors, these five subtypes of muscarinic receptors share a structural feature common to such receptors—a long, “serpentine” polypeptide chain that crosses the cell membrane seven times (illustrated for G protein receptors in Chapter 2). Table 5.2 summarizes the muscarinic receptor subtypes, including their predominant location and the type of G protein with which they are coupled. Additional details about muscarinic receptor location and function in the pulmonary system are presented in the final section of this chapter, which summarizes nervous control and receptors in the lung.

Cholinergic Agents

Cholinergic drugs mimic the action caused by Ach at receptor sites in the parasympathetic system and neuromuscular junction.

• **Fig. 5.4** Location of muscarinic and nicotinic receptor sites in the peripheral nervous system. *M-Ach*, Muscarinic site; *N-Ach*, nicotinic site; *NE*, norepinephrine.



Such agents can cause stimulation at the terminal nerve site (neuroeffector junction) by two distinct mechanisms, leading to their classification as direct acting or indirect acting. Table 5.3 lists cholinergic agents, categorized as direct acting or indirect acting, and their clinical uses. The terms *cholinergic*, *cholinoceptor stimulant*, and *cholinomimetic* are broader than *parasympathomimetic* and denote agents stimulating Ach receptors located in the parasympathetic system (muscarinic) or other sites, such as the neuromuscular junction (nicotinic). A cholinergic drug can activate muscarinic and nicotinic receptors.

Direct-Acting Cholinergic Agents

Direct-acting cholinergic agents are structurally similar to Ach. As shown in Fig. 5.3, direct-acting cholinergic agents mimic Ach, binding and activating muscarinic or nicotinic receptors directly. Examples of this group include methacholine, carbachol, bethanechol, and pilocarpine. Methacholine has been used in bronchial challenge tests by inhalation to assess the degree of airway reactivity in patients with asthma and others. The parasympathetic effect is bronchoconstriction. Methacholine is a useful diagnostic agent to detect differences in degree of airway reactivity

between individuals without asthma and those with asthma and, thus, hyperreactive airways.

Indirect-Acting Cholinergic Agents

KEY POINT

Parasympathomimetic, or cholinergic, agonists are divided into *direct-acting* agents (e.g., methacholine), which resemble Ach and stimulate cholinergic receptors directly, and *indirect-acting* agents (e.g., neostigmine), which inhibit the enzyme cholinesterase and allow increased Ach transmission. A typical *parasympatholytic*, or *anticholinergic*, agent is atropine.

Indirect-acting cholinergic agonists inhibit the cholinesterase enzyme, as shown in Fig. 5.3. Because cholinesterase usually inactivates the Ach neurotransmitter, inhibiting this enzyme results in accumulation of endogenous Ach at the neuroeffector junction of parasympathetic nerve endings or the neuromuscular junction. More Ach is made available to attach to receptor sites and to stimulate cholinergic responses. If Ach receptors have been blocked, this increase in neurotransmitter can reverse the blockage by competing with the blocking drug for the receptors. Nerve transmission can then resume, either at the parasympathetic terminal site or at the neuromuscular junction.

The drug echothiophate (Phospholine), included in Table 5.3, stimulates autonomic muscarinic receptors in the iris sphincter and ciliary muscle of the eye to produce pupillary constriction (*miosis*) and lens thickening. An increase in the neurotransmitter Ach at the neuromuscular junction makes some drugs, such as neostigmine, useful in reversing neuromuscular blockade caused by paralyzing agents, such as pancuronium or doxacurium (see Chapter 18). Neostigmine is useful in increasing muscle strength in a neuromuscular disease, such as myasthenia gravis, in which the cholinergic receptor is blocked by autoantibodies. The drug edrophonium (Tensilon) was used to determine whether muscle weakness is caused by overdosing with an indirect-acting cholinergic agent (causing ultimate receptor fatigue and blockade) or undertreatment with an insufficient drug. However, due to high rates of false-positive results and the development of serological antibody testing as the gold standard for the diagnosis of myasthenia gravis, it was discontinued in the United States.

When using indirect-acting cholinergic agents, such as neostigmine, to increase nerve function at the neuromuscular junction,

TABLE 5.2 Muscarinic Receptor Subtypes, Location, and G-Protein Linkage

Muscarinic Receptor Type	Location	G-Protein Subtype
M ₁	Parasympathetic ganglia, nasal submucosal glands	G _q
M ₂	Heart, postganglionic parasympathetic nerves	G _i
M ₃	Airway smooth muscle, submucosal glands	G _q
M ₄	Postganglionic cholinergic nerves, possible effect on CNS, decrease in locomotion	G _i
M ₅	Possible effect on CNS	G _q

CNS, Central nervous system.

TABLE 5.3 Examples of Direct-Acting and Indirect-Acting Cholinergic Agents

Category	Generic Name	Brand Name	Clinical Uses
Direct-acting	Acetylcholine chloride	Miochol-E	Ophthalmic miotic, glaucoma
	Carbachol	Miostat	Ophthalmic miotic, glaucoma
	Pilocarpine hydrochloride	Isopto Carpine, Salagen, Vuity	Ophthalmic miotic, glaucoma
	Methacholine	Provocholine	Diagnostic, asthma
	Bethanechol	Duvoid	Treatment of urinary retention
Indirect-acting	Echothiophate iodide	Phospholine Iodide	Ophthalmic miotic, glaucoma
	Pyridostigmine	Mestinon, Regonol	Muscle stimulant, myasthenia gravis, reversal of nondepolarizing muscle relaxants
	Neostigmine methylsulfate	Bloxiverz	Muscle stimulant, myasthenia gravis, reversal of nondepolarizing muscle relaxants

Ach activity at parasympathetic sites, such as salivary and nasopharyngeal glands, also increases. These undesirable muscarinic effects can be blocked by pretreatment with a parasympatholytic or antimuscarinic drug, such as atropine or its derivatives.

Cholinesterase Reactivator (Pralidoxime)

Organophosphates, such as parathion and malathion and the drug echothiophate, form an irreversible bond with cholinesterase (also called *acetylcholinesterase*). Organophosphates are used as insecticides, and occasionally patients present with toxic exposure and absorption. The effects of these agents can be lethal, and because of this, they have also been used as a biologic weapon (“nerve gas”). Because they affect Ach, they have an effect on neuromuscular function and muscarinic receptors; there is initial stimulation, followed by blockade if a high enough dosage is absorbed. Muscle weakness and paralysis can result.

The bonding of irreversible inhibitors with cholinesterase is slow, taking up to 24 hours. Once formed, however, the duration is limited only by the body’s ability to produce new cholinesterase, which takes 1 to 2 weeks. A cholinesterase reactivator, such as pralidoxime chloride (Protopam Chloride), can be used in the treatment of organophosphate toxicity in the first 24 hours. After this time, the bonding of cholinesterase and cholinesterase inhibitors cannot be reversed, but atropine (a parasympatholytic) can be used to block the overly available Ach neurotransmitter at the receptor sites. Support of ventilation and airway maintenance would be required for the duration of the effects.

Anticholinergic Agents

Anticholinergic agents block Ach receptors and act as cholinergic antagonists. Parasympatholytic (antimuscarinic) agents, such as atropine, and drug classes, such as neuromuscular blockers and ganglionic blockers, are anticholinergic because they block Ach at their respective sites. However, a neuromuscular or ganglionic blocking agent would *not* be considered a parasympatholytic or antimuscarinic agent because the site of action is not within the parasympathetic system. Parasympatholytic agents are antimuscarinic because of the limitation to parasympathetic terminal fiber sites.

Atropine as a Prototype Parasympatholytic Agent

Atropine is usually considered the prototype parasympatholytic, and there is renewed interest in the use of aerosolized analogs of atropine in respiratory care; this is discussed more fully in [Chapter 7](#). Atropine occurs naturally as the levo isomer in *Atropa belladonna*, or nightshade, and in *Datura stramonium*, or jimsonweed. The drug is referred to as a *belladonna alkaloid*.

Atropine is a *competitive antagonist* to Ach at muscarinic receptor sites (i.e., glands, gastrointestinal tract, heart, and eyes) and can form a reversible bond with these cholinergic receptors. It is nonspecific for muscarinic receptor subtypes and blocks M_1 , M_2 , and M_3 receptors. Atropine blocks salivary secretion and causes dry mouth. In the respiratory system, atropine decreases secretion by mucous glands and relaxes the bronchial smooth muscle by blocking parasympathetically maintained basal tone. Atropine blocks vagal innervation of the heart to produce increased heart rate. There is no effect on blood vessels because these do not have parasympathetic innervation; only the Ach receptors do. Vascular resistance would not increase with atropine. If a

parasympathomimetic *were* given, atropine would block the dilating effect on blood vessel receptor sites. Pupillary dilation (*mydriasis*) occurs as a result of blockade of the circular iris muscle, and the lens is flattened (*cycloplegia*) by blockade of the ciliary muscle. In the gastrointestinal tract, atropine decreases acid secretion, tone, and mobility. Bladder wall smooth muscle is relaxed, and voiding is slowed. Sweating is inhibited by atropine, which blocks Ach receptors on sweat glands. Sweat glands are innervated by sympathetic cholinergic fibers.

At usual clinical doses, atropine exerts a low level of CNS stimulation, with a slower sedative effect in the brain. Scopolamine, another classic antimuscarinic agent, can produce drowsiness and amnesia. In larger doses, atropine can cause toxic effects in the CNS, including hallucinations.

The anticholinergic (antimuscarinic) effect on the vestibular system can inhibit motion sickness. Scopolamine was used for this, and antihistamine drugs, such as dimenhydrinate (Dramamine), which have anticholinergic effects, are commonly used to prevent motion sickness. The dry mouth and drowsiness that also occur with a drug, such as dimenhydrinate, are typical antimuscarinic effects.

Parasympatholytic (Antimuscarinic) Effects

If the basic effects of the parasympathetic system are known, the effects of an antagonist, such as atropine, can be deduced. For example, if parasympathetic (vagal) stimulation slows the heart rate, parasympatholytic should increase the heart rate by blocking that innervation. [Box 5.1](#) lists the effects and uses of parasympatholytic agents.

Sympathetic Branch

KEY POINT

Sympathetic effects on the cardiopulmonary system include increased heart rate and contractile force, increased blood pressure, bronchodilation, and probable increased secretion from mucous glands in the airway.

As noted in the general description of the parasympathetic and sympathetic branches of the autonomic nervous system, sympathetic (adrenergic) effects are mediated both by neurotransmitter release from sympathetic nerves and by the release of circulating catecholamines (i.e., norepinephrine and epinephrine) from the adrenal medulla. Circulating catecholamines stimulate adrenergic receptors throughout the body, not just receptors with nerve fibers present. Sympathetic activation results in stimulation of the heart, increased cardiac output, increased blood pressure, mental

• BOX 5.1 Uses and Effects of Parasympatholytic (Antimuscarinic) Agents

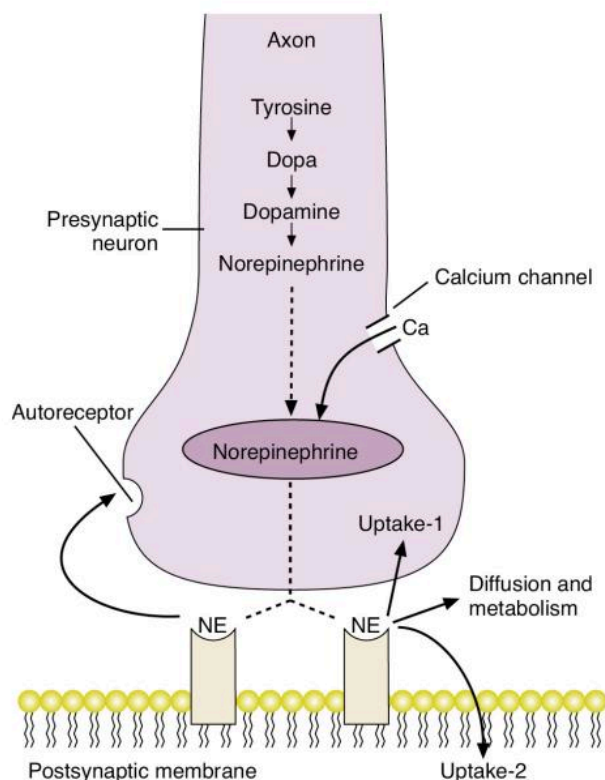
- Bronchodilation
- Preoperative drying of secretions
- Antidiarrheal agent
- Prevention of bed-wetting in children (increase in urinary retention)
- Treatment of peptic ulcer
- Treatment of organophosphate poisoning
- Treatment of mushroom (*Amanita muscaria*) ingestion
- Treatment of bradycardia

stimulation, accelerated metabolism, and bronchodilation in the pulmonary system.

Adrenergic Neurotransmitter Function

In the sympathetic branch of the autonomic nervous system, the usual neurotransmitter at the terminal nerve sites is norepinephrine, with the exceptions described previously (sweat glands and adrenal medulla). Fig. 5.5 illustrates neurotransmitter function with norepinephrine. In the presynaptic neuron, tyrosine is converted to dopa and then to dopamine, which is converted by dopamine β -hydroxylase to norepinephrine in the storage vesicles. An action potential in the nerve opens calcium channels, allowing an influx of calcium. Increased intracellular calcium leads to exocytosis of the vesicles containing norepinephrine, which attach to receptors on the postsynaptic membrane. The exact physiologic effect depends on the site of innervation and the type of sympathetic receptor, which can also vary, as described below.

The primary method of terminating the action of norepinephrine at the postsynaptic membrane is through a reuptake process that brings norepinephrine back into the presynaptic neuron. This is termed *uptake-1*. The neurotransmitter action can be ended by two other mechanisms as well: (1) uptake into tissue sites around the nerve terminal, a process termed *uptake-2* to distinguish it from reuptake into the nerve terminal itself; and (2) diffusion of excess norepinephrine away from the receptor site, to be metabolized in the liver or plasma. In addition, norepinephrine can stimulate *autoreceptors* on the presynaptic neuron, which inhibits



• **Fig. 5.5** Adrenergic nerve transmission mediated by the neurotransmitter norepinephrine (NE). The action of the neurotransmitter is terminated primarily by a reuptake mechanism (uptake-1) and by enzyme metabolism and a second uptake mechanism into tissue sites (uptake-2). Norepinephrine attaches to autoreceptor sites on the presynaptic neuron to inhibit further neurotransmitter release. Ca, Calcium ion.

further neurotransmitter release. These autoreceptors have been identified as α_2 -receptors (discussed later).

The distinction between the two types of uptake processes is a result of research published by Iversen in 1965.¹ The uptake-2 process is a mediated uptake of exogenous amines (chemicals, such as norepinephrine) in *nonneuronal* tissues, such as cardiac muscle cells. Iversen and Salt² distinguished details of the uptake-2 process:

- It is a mediated transport system.
- It is a low-affinity but high-capacity system.
- It is not as stereochemically specific as uptake-1.
- It is specific to catecholamines.
- The order of affinity for uptake of specific agents, in *decreasing* order, is as follows: isoproterenol > epinephrine > norepinephrine.
- Certain corticosteroids can inhibit the uptake-2 process, potentiating catecholamines.

The last effect of uptake-2 inhibition by corticosteroids is discussed more fully in Chapter 11. Table 5.4 lists the physiologic effects of sympathetic activation. The effects listed in Table 5.4 are given for the same organs listed in Table 5.1 for the parasympathetic system for comparison.

Enzyme Inactivation

The enzymes that metabolize norepinephrine, epinephrine, and chemicals similar to these neurotransmitters are important for understanding the differences in the action of the adrenergic bronchodilator group. Chemicals structurally related to epinephrine are termed *catecholamines*, and their general structure is outlined in Chapter 6 in the discussion of sympathomimetic (adrenergic) bronchodilators. Two enzymes that can inactivate catecholamines, such as epinephrine, are available: (1) catechol *O*-methyltransferase (COMT) and (2) monoamine oxidase (MAO). The action of both enzymes on epinephrine (Fig. 5.6) is important because COMT is responsible for ending the action of catecholamine bronchodilators.

Sympathetic (Adrenergic) Receptor Types

The effects of adrenergic receptors are mediated by coupling with G proteins, and they are identified as G protein–linked receptors. Adrenergic receptor subtypes, with examples of their location and the type of G protein with which they are coupled, are summarized in Table 5.5.

α and β Receptors

KEY POINT

Receptors at sympathetic end sites are subdivided into α and β receptors, with α receptors mediating excitatory effects (e.g., vasoconstriction) and β receptors mediating inhibitory effects (e.g., smooth muscle relaxation).

In 1948, Ahlquist³ distinguished *alpha* (α) and *beta* (β) sympathetic receptors on the basis of differing responses to various adrenergic drugs, all of which were similar to norepinephrine with minor structural differences. These drugs included phenylephrine, norepinephrine, epinephrine, and isoproterenol. The two types of sympathetic receptors were distinguished as follows:

- **α Receptors:** Generally *excite*, with the exception of the intestine and CNS receptors, where inhibition or relaxation occurs
- **β Receptors:** Generally *inhibit or relax*, with the exception of the heart, where stimulation occurs

TABLE 5.4 Effects of Sympathetic (Adrenergic) Stimulation on Selected Organs or Sites*

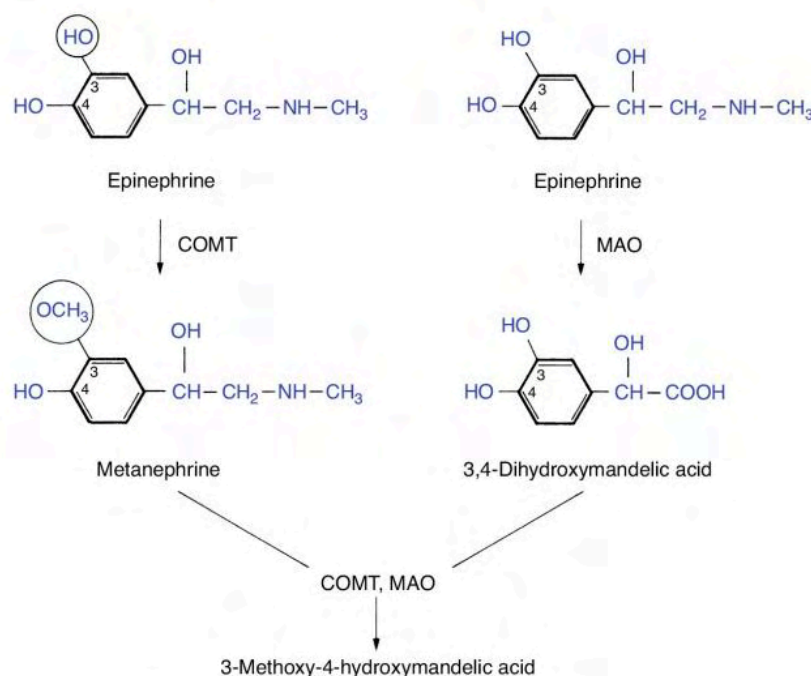
Organ/Site	Sympathetic (Adrenergic) Response	Organ/Site	Sympathetic (Adrenergic) Response
Heart		Eye	
SA node	Increase in rate	Iris radial muscle	Contraction (mydriasis)
Contractility	Increase in force	Iris circular muscle	None
Conduction velocity	Increased AV node conduction	Ciliary muscle	Relaxation for far vision†
Bronchi		Gastrointestinal Tract	
Smooth muscle	Relaxation and dilation of airway diameter	Decreased motility	
Mucous glands	Increased secretion	Gastrointestinal Sphincters	
Vascular Smooth Muscle		Contraction	
Skin and mucosa	Vasoconstriction	Urinary Bladder	
Pulmonary	Dilation/constriction (two types of sympathetic receptors)	Detrusor	Relaxation
Skeletal muscle	Dilation (predominantly)	Trigone sphincter	Contraction
Coronary	Dilation/constriction (two types of sympathetic receptors)	Sweat Glands	
Salivary Glands		Increased secretion‡	
Skeletal Muscle		Glycogenolysis	
	Increased contractility	Skeletal muscle	Increased
		Lipolysis (Multiple Sites)	
		Increased	
		Renin Secretion (Kidney)	
		Increased	
		Insulin Secretion (Pancreas)	
		Decreased	

*Effects of sympathetic activation are mediated by direct innervation of nerve fibers and by circulating epinephrine released from the adrenal medulla.

†Relaxes as a result of circulating epinephrine, with sympathetic activation.

‡Innervated by sympathetic nerves with *acetylcholine* neurotransmitter (cholinergic receptors); response to exogenous cholinergic agent is increased sweating.

AV, Atrioventricular; SA, sinoatrial.



• **Fig. 5.6** Metabolic pathways for the transformation of epinephrine by the enzymes catechol O-methyltransferase (COMT) and monoamine oxidase (MAO) to an inactive form.

α -Sympathetic receptors are found on peripheral blood vessels, and stimulation results in vasoconstriction. α -Adrenergic agonists are frequently used for topical vasoconstriction of the nasal mucosa to treat symptoms of nasal congestion caused by the common cold. β -Adrenergic receptors are found on airway smooth muscle and in the heart. Drug activity of adrenergic stimulants (sympathomimetics) ranges along the spectrum seen in Fig. 5.7.

As illustrated in Fig. 5.7, phenylephrine is one of the purest α stimulants, and isoproterenol is an almost-pure β stimulant. “Pure” reactions do not occur with any drug—that is, even phenylephrine may affect other sites. Epinephrine stimulates α and β sites equally, but norepinephrine has more of an α effect than a β effect.

β_1 and β_2 Receptors

In 1967, Lands et al.⁴ further differentiated β receptors into β_1 and β_2 subtypes. β_1 Receptors are found in cardiac muscle, and β_2 receptors (which encompass all other β receptors) are found in bronchial, vascular, and skeletal muscles. The distinction among types of β receptors is as follows:

- β_1 Receptors: Increase the rate and force of cardiac contraction
- β_2 Receptors: Relax bronchial smooth muscle and vascular beds of skeletal muscle

KEY POINT

β receptors are subdivided into β_1 receptors, which are excitatory and found in the heart, and β_2 receptors, which are found elsewhere and mediate inhibitory responses.

β_1 receptors constitute the exception to the general rule that β receptors cause relaxation. β_2 receptors form the basis for the class of adrenergic bronchodilators, which act to relax bronchial smooth muscle by stimulation of these receptors. β receptor, briefly characterized as an example of a G protein–linked receptor in Chapter 2 in the introduction to *pharmacodynamics* (drug–receptor interaction), is discussed in more detail in Chapter 6, which discusses β -adrenergic bronchodilators. A third type of β receptor, the β_3 receptor, has also been distinguished as a β -receptor type found on lipocytes (fat cells) whose stimulation results in lipolysis.

α_1 and α_2 Receptors

KEY POINT

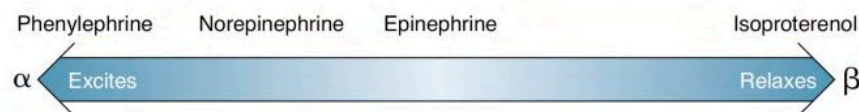
α receptors are subdivided into α_1 receptors, which are excitatory, and α_2 receptors, which are inhibitory and are found on the presynaptic neuron to inhibit further neurotransmitter release.

α receptors have also been differentiated into α_1 and α_2 receptors. This classification has been made on a *morphologic* basis (location of the receptors) and a *pharmacologic* basis (differences in response to various drugs). The pharmacologic differentiation of α_1 and α_2 receptors is similar to the distinction between α and β receptors (Fig. 5.8). This differentiation is based on a response continuum ranging from excitation (α_1) to inhibition (α_2) as different drugs are administered. For example, phenylephrine causes vasoconstriction, as previously mentioned, whereas clonidine (Catapres) causes a lowering of blood pressure and sympathetic activity. Both

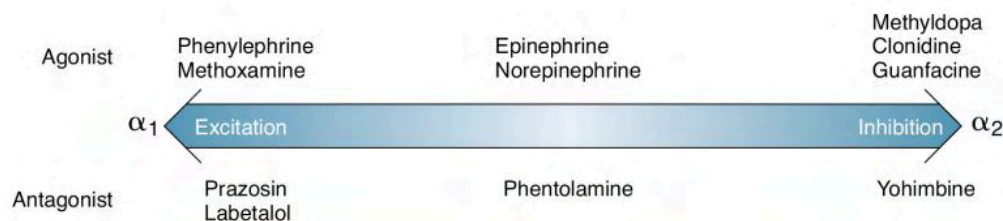
TABLE 5.5 Adrenergic Receptor Subtypes: Location and G-Protein Linkage

Receptor Type	Location	G-Protein Subtype
α_1	Peripheral blood vessels	G_q
α_2	Presynaptic sympathetic neurons (autoreceptor), CNS	G_i
β_1	Heart	G_s
β_2	Smooth muscle (including bronchial), cardiac muscle	G_s
β_3	Lipocytes	G_s

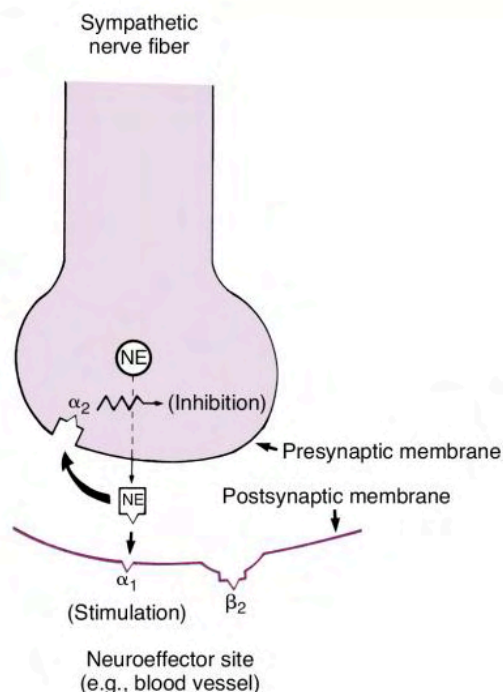
CNS, Central nervous system.



• **Fig. 5.7** Spectrum of activity of adrenergic agonists, ranging from excitatory effects to inhibitory effects, by which α and β receptors are distinguished.



• **Fig. 5.8** Spectrum of activity of α -receptor agonists and antagonists, from excitatory to inhibitory. Epinephrine and norepinephrine can stimulate α_1 -receptor and α_2 -receptor sites. For example, phenylephrine stimulates α_1 receptors and causes vasoconstriction, whereas methyldopa stimulates α_2 receptors and can decrease blood pressure, although both are α -receptor agonists. Prazosin is a selective α_1 -blocking agent, and yohimbine is a selective α_2 -blocking agent.



• **Fig. 5.9** Location and effect of α_2 receptors, also designated *autoreceptors*. Stimulation of α_2 receptors by norepinephrine (NE) on the presynaptic neuron inhibits further neurotransmitter release and nerve action.

agents are considered α -receptor agonists. Other agents, such as prazosin (Minipress) or labetalol (Normodyne), cause lowering of blood pressure, but yohimbine causes increase in blood pressure. Yet *all* of these agents are considered α -receptor antagonists. Blockade of α_1 -excitatory receptors by prazosin would prevent vasoconstriction and decrease blood pressure, whereas blockade of α_2 -inhibitory receptors by yohimbine would prevent vasodilation and increase blood pressure.

Because different α agonists can cause opposite effects, and different α blockers do the same, α receptors were subdivided into the two types described. The location-based, or morphologic, differentiation of α_1 and α_2 receptors is more complex. In *peripheral* nerves, α_1 receptors are located on postsynaptic sites, such as vascular smooth muscle, and α_2 receptors are presynaptic (Fig. 5.9). Stimulation of these peripheral α_1 receptors causes excitation and vasoconstriction; activation of peripheral (presynaptic) α_2 receptors causes inhibition of further neurotransmitter release. Peripheral α_2 receptors perform a negative feedback control mechanism, referred to as *autoregulation*, which has been shown with sympathetic (adrenergic) neurons; they are referred to as *autoreceptors*⁵ (see Fig. 5.5). Norepinephrine released from the nerve ending can activate α_1 (postsynaptic) and α_2 (presynaptic) receptors. Postsynaptic stimulation causes a cell response, such as vasoconstriction, but presynaptic stimulation leads to inhibition of further neurotransmitter release. In the CNS, α_2 receptors are generally considered to be located on postsynaptic sites; this is the reverse of their location peripherally, where they are presynaptic. These central postsynaptic α_2 receptors are the site of action for antihypertensive agents, such as clonidine (Catapres) or methyl dopa (Aldomet). These are discussed further and illustrated in Chapter 22.

To summarize, α_1 and β_1 receptors *excite*, and α_2 and β_2 receptors *inhibit*. This consistency of subscripts for (1) excitation versus (2) inhibition aids in remembering their effects.

Dopaminergic Receptors

Other receptors in the CNS (brain) respond to dopamine, a chemical precursor of norepinephrine and are, therefore, termed *dopaminergic*. Because dopamine is chemically similar to epinephrine and stimulates α and β receptors, dopaminergic receptors are classified as a type of adrenergic receptor.

Sympathomimetic (Adrenergic) and Sympatholytic (Antiadrenergic) Agents

Drugs that stimulate the sympathetic system and produce adrenergic effects (sympathomimetics) and drugs that block adrenergic effects (sympatholytics) are discussed in greater detail in separate chapters. In this book, emphasis is placed on β -adrenergic agonists used for bronchodilation (see Chapter 6) and on adrenergic agonists used for cardiovascular effects, such as cardiac stimulation (see Chapter 21) or vasoconstriction (see Chapter 22). Adrenergic blocking agents are considered for their antihypertensive and antianginal effects (see Chapter 22). To exemplify both sympathomimetic and sympatholytic agents, Table 5.6 provides selected examples of drugs categorized as agonists or antagonists of the sympathetic system and includes their generic names, brand names, and common clinical uses.

Neural Control of Lung Function

Both the sympathetic and parasympathetic branches of the autonomic nervous system exert control of lung function. At present, the two branches form the basis for two classes of respiratory care drugs that modify airway smooth muscle tone: (1) the adrenergic bronchodilator group and (2) the anticholinergic bronchodilator group.

Lung function includes more than just airway smooth muscle tone. Multiple sites and tissues are involved in lung function, as follows:

- Airway smooth muscle
- Submucosal and surface secretory cells
- Bronchial epithelium
- Pulmonary and bronchial blood vessels

In addition to autonomic nerve fibers and the receptors associated with them, sites in the lung (smooth muscle, glands, and vascular beds) may be affected by release of mediators from inflammatory cells, such as mast cells and platelets, or by release of epithelial factors, such as a relaxant factor, which can reduce airway contractility in response to spasmogens, such as histamine, serotonin, or Ach.⁶ Receptors in the lung and airways for mediators released by inflammatory cells include the following:

- *Histamine receptors*: Especially the H_1 type
- *Prostaglandin receptors*: Such as prostacyclin, prostaglandin D_2 (PGD_2), prostaglandin $F_2\alpha$ ($PGF_2\alpha$), and thromboxane A_2
- *Leukotriene receptors*: Such as LTB_4 and the C_4 - D_4 - E_4 series that comprise what was formerly termed *slow-reacting substance of anaphylaxis* (SRS-A)
- *Platelet-activating factor (PAF) receptors*
- *Adenosine receptors*: Such as A_1 and A_2
- *Bradykinin receptors*

The mediators of inflammation and their receptors (e.g., histamine and prostaglandins) are discussed in the review of corticosteroids (see Chapter 11) and other antiasthma drugs (see Chapter 12) intended to inhibit or prevent an inflammatory response in the lung.

TABLE 5.6 Examples of Adrenergic Agonists and Antagonists

Category	Generic Name	Brand Name	Uses
Sympathomimetic	Epinephrine	Adrenalin	Bronchodilator, cardiac stimulant, vasoconstrictor
	Ephedrine	Sudafed, various	Nasal decongestant
	Dextroamphetamine	Adderall, Dexedrine	CNS stimulant
	Dopamine	Intropin	Vasopressor, shock syndrome
	Albuterol	Proventil, Ventolin, Pro Air	Bronchodilator
	Salmeterol	Serevent	Bronchodilator
Sympatholytic	Phentolamine	Oraverse	Vasodilator, pheochromocytoma, reverse effects of local anesthetics on lip and tongue after dental procedures
	Prazosin	Minipress	Antihypertensive
	Labetalol	Tandate	Antihypertensive
	Metoprolol	Lopressor, Toprol-XL, Kapsargo Sprinkle	Antihypertensive, antianginal
	Propranolol	Inderal, Innopran-XL, Hemangeol	Antihypertensive, antiarrhythmic (PAT)
	Timolol	Betimol, various	Ophthalmic solution, treat increased IOP in patients with glaucoma
	Esmolol	Brevibloc	Antiarrhythmic

CNS, Central nervous system; IOP, intraocular pressure; PAT, paroxysmal atrial tachycardia.

Sympathetic Innervation and Effects

The sympathetic nervous system exerts its effects by direct and indirect means, as outlined in previous sections. *Direct effects* refer to direct innervation of tissue sites by nerve fibers. *Indirect effects* are mediated by the release of the circulating catecholamines epinephrine and norepinephrine.

Sympathetic nerve fibers form ganglionic synapses outside the lung. Postganglionic sympathetic nerve fibers from the cervical and upper thoracic ganglia form plexuses at the hilar region of the lung and enter the lung mingled with parasympathetic nerves. Histochemical and ultrastructural studies show a relatively high density of sympathetic nerve fibers attaching to submucosal glands and bronchial arteries but few or no nerve fibers leading to airway smooth muscle in the human lung.⁷ Fig. 5.10 illustrates sympathetic innervation and effects mediated directly by nerve action and indirectly by circulating epinephrine in the human lung.

Airway Smooth Muscle

There is little or no direct sympathetic innervation of airway smooth muscle in the human lung.⁸ The sympathetic nervous system controls bronchial smooth muscle tone by circulating epinephrine and norepinephrine, which act on α and β receptors on airway smooth muscle. Recall that epinephrine stimulates both α and β receptors, whereas norepinephrine acts primarily on α receptors.

β Receptors. β receptors mediate relaxation of airway smooth muscle. This action is mimicked by the class of β -adrenergic bronchodilators, introduced in Chapter 6. β receptors are distributed from the trachea to the terminal bronchioles; the density of these receptors increases as the airway diameter becomes smaller. β agonists can cause relaxation of small airways.

β_2 receptors traditionally have been identified as the β -receptor subtype on airway smooth muscle; this has been further verified for the human lung by autoradiographic studies and molecular gene studies.⁹ There is species variation for the presence of

β -receptor subtypes, however, with β_1 and β_2 receptors present in guinea pig and dog airways.

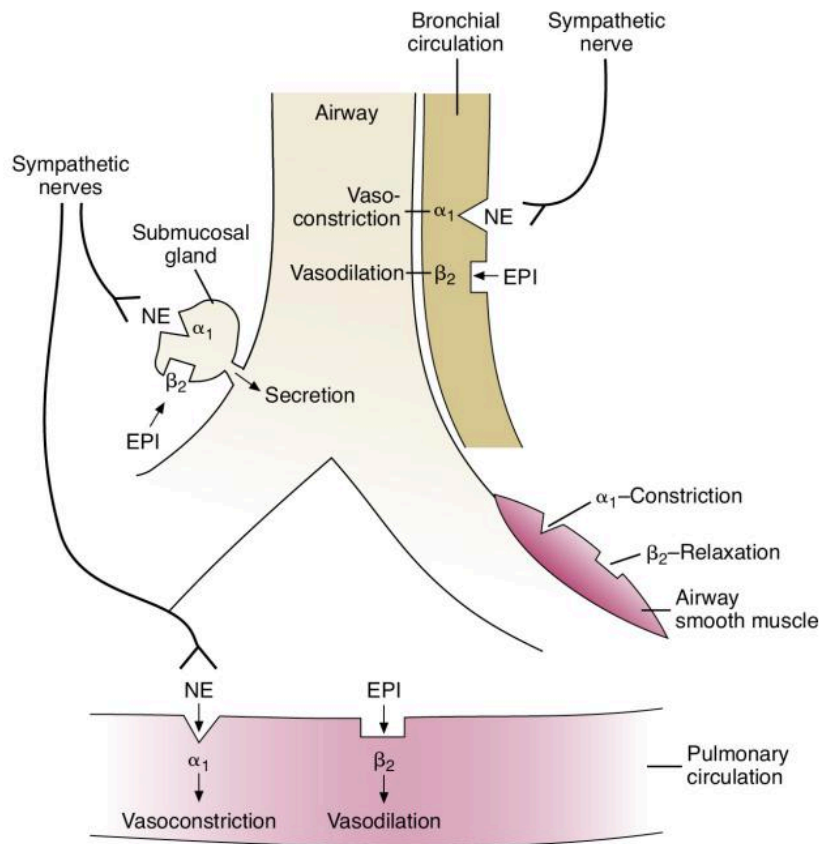
β_1 and β_2 receptors in the lung have also been distinguished as *neuronal* and *hormonal* receptors, respectively. This is based on the concept that β_1 receptors are β receptors for sites where norepinephrine is released from sympathetic nerve terminal fibers (neuronal); β_2 receptors are β receptors responsive to circulating epinephrine (hormonal). Both receptors cause airway smooth muscle relaxation when stimulated, either by sympathetic nerve release of norepinephrine or by circulating epinephrine, in such species as the dog or the guinea pig, which have β_1 receptors on airway smooth muscle.¹⁰ In the human lung, which has no sympathetic innervation of airway smooth muscle, adrenergic receptors are all of the β_2 type; β_1 receptors have been identified by radioligand binding and autoradiographic studies of alveolar walls in the lung periphery.⁹ Using this terminology, relaxation of human airway smooth muscle would be accomplished by stimulation of hormonal β receptors via circulating or exogenous catecholamines. β_3 receptors, which have also been identified on lipocytes, have no known function in the human airway.¹¹

CLINICAL CONNECTION

Albuterol is a β_2 specific agent that works on β_2 receptors. This stimulation causes bronchodilation of airway smooth muscle. However, β_1 receptor stimulation is possible and respiratory therapists must monitor heart rate during use of a β agonist.

α Receptors. α receptors exist in the human lung in less quantity than β receptors and with no difference in distribution between large and small airways. Norepinephrine stimulates α receptors, but their effect in the airway seems to be minor. Evidence of sympathetic-induced bronchoconstriction has been provided by studies in which lung tissue was treated with a β blocker, or antagonist (e.g., propranolol), and then exposed to epinephrine, which stimulates α and β receptors.¹² Because β receptors were blocked, epinephrine was attached to the free α receptors; the result was contraction of smooth muscle, providing evidence of

• **Fig. 5.10** Adrenergic control mechanisms, including adrenergic receptor subtypes and effects in the pulmonary system. Sites of direct sympathetic nerve innervation, such as the pulmonary vasculature, are indicated. Other sites, such as airway smooth muscle, lack nerve innervation but respond to circulating epinephrine (EPI) released by the adrenal medulla with sympathetic activation and can respond to exogenous catecholamines. NE, Norepinephrine.



the existence of α receptors and showing a contractile effect. The clinical use of α receptor–blocking agents, such as dibenamine, thymoxamine, and phentolamine, in cases of status asthmaticus has been reported for more than 40 years, lending support to the role of α receptors in bronchial contraction.¹³ The role of α receptors in controlling airway smooth muscle remains the subject of investigation.

CLINICAL CONNECTION

In patients with airway edema (i.e., stridor, croup) α receptor stimulation from inhaled racemic epinephrine provides vasoconstriction resulting in improvement of the edema. Additionally, α receptor stimulation occurs with the use of pseudoephedrine as a result of a “stuffy” nose (i.e., nasal edema).

Lung Blood Vessels

Blood flow in the lung is made up of two different systems: the *pulmonary* and the *bronchial* circulations. The pulmonary circulation receives the body’s venous return from the right heart and is critical for gas exchange. The bronchial circulation is an arterial supply that perfuses lung tissue to supply nutrients and remove metabolic by-products.

The pulmonary circulation is innervated by parasympathetic and sympathetic nerves. Sympathetic nerves release norepinephrine to stimulate α receptors and cause vascular contraction. β receptors on pulmonary blood vessels cause relaxation and are stimulated by circulating epinephrine. An exogenous catecholamine can cause vasoconstriction, dilation, or no effect, depending on the relative stimulation of receptor types.

The bronchial circulation is innervated predominantly by sympathetic nerves. Activation of sympathetic nerves causes

vasoconstriction mediated by α receptors. Stimulation of β receptors by circulating epinephrine causes relaxation and vasodilation of bronchial blood vessels.

Mucous Glands

Human bronchial submucosal glands are innervated by sympathetic and parasympathetic nerves. α and β receptors are present on tracheal submucosal glands. Stimulation of these receptors causes an increase in secretion of fluid and mucus. Epithelial cells on the airway lining do not have direct sympathetic innervation but do possess β_2 receptors, whose stimulation can also increase secretion of fluid. Mucociliary clearance is enhanced, removing trapped particulate matter.¹⁴

Parasympathetic Innervation and Effects

KEY POINT

In the human lung, glands and blood vessels are innervated by sympathetic nerve fibers, but airway smooth muscle has few, if any, such fibers, responding instead to circulating epinephrine by means of β receptors. Parasympathetic vagal nerves innervate the lung as well, supplying airway smooth muscle and mucous glands.

The lung is supplied by vagus nerves, with the recurrent laryngeal nerve (part of the thoracic vagus) innervating the trachea; other branches of the vagus enter the lung at the hilum and innervate the intrapulmonary airways. In the trachea and remaining airways, parasympathetic nerves supply airway smooth muscle and glands. Vagus nerves in the lung release Ach and are termed *cholinergic*. Ach couples with muscarinic Ach receptors on airway smooth muscle to cause bronchoconstriction and on submucosal

glands to stimulate secretion. The action of Ach is limited by the enzyme acetylcholinesterase, or cholinesterase, which breaks down Ach.

Cholinergic nerve fibers in the lung are densest in the hilar region and decrease in density toward the airway periphery. Cholinergic muscarinic receptors also decrease in density in distal airways. Electrical stimulation of vagus nerves in dog studies caused more contraction in the intermediate bronchi than in the main bronchi or trachea.¹⁵

Muscarinic Receptors in the Airway

The genes for five subtypes of Ach, or muscarinic, receptors have been identified, designated M_1 through M_5 . Only four of these subtypes, M_1 to M_4 , have been identified by chemical (ligand) binding studies pharmacologically. Three of these muscarinic receptor subtypes have been identified in the human lung: M_1 , M_2 , and M_3 . Their locations are illustrated in Fig. 5.11, and the function of each is discussed.

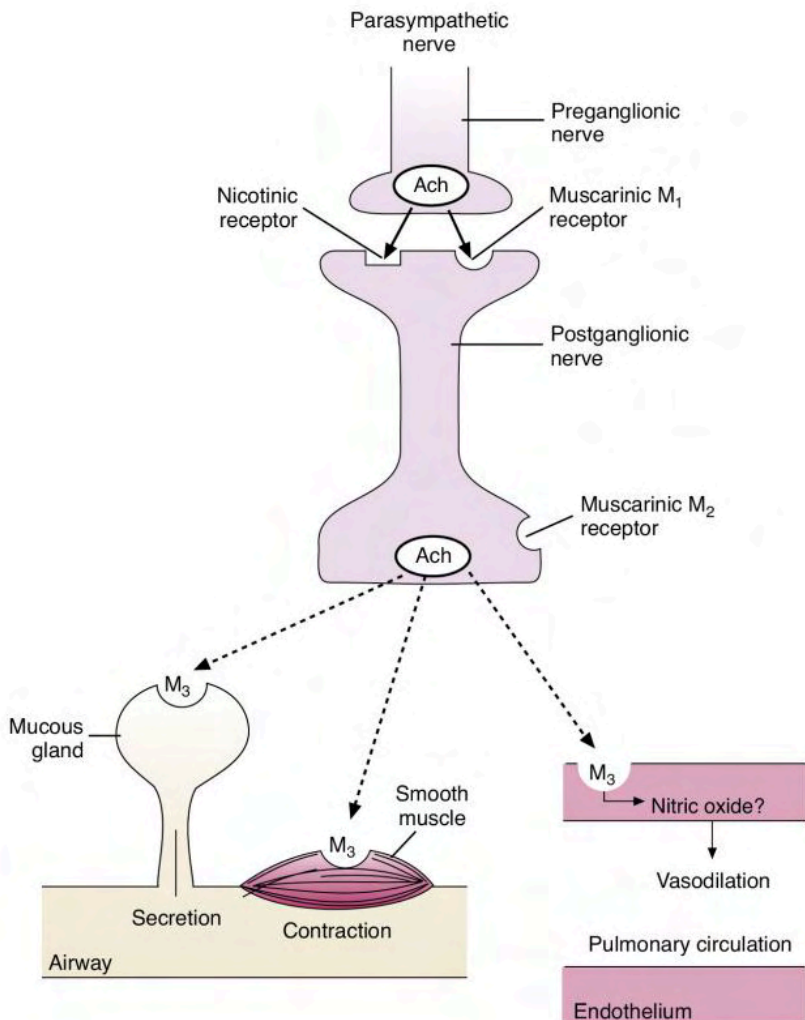
M_1 Receptors. M_1 receptors are present at the parasympathetic ganglion on the postjunctional membrane. Usually, Ach ganglionic receptors are nicotinic, as described previously. However, the M_1 receptor may facilitate nicotinic receptor activity and nerve transmission, with an overall excitatory effect.

M_2 Receptors. M_2 receptors are localized to the presynaptic membrane of postganglionic parasympathetic nerve endings. These

receptors are thought to be autoregulatory receptors whose stimulation by Ach inhibits further Ach release from the nerve ending, thereby limiting the cholinergic stimulation. This is analogous to the α_2 receptor inhibiting further release of norepinephrine from sympathetic nerve endings, which identifies it as an autoreceptor, as discussed previously (see section “Cholinergic Neurotransmitter Function”). Stimulation of prejunctional M_2 receptors in human airways in vitro results in strong inhibition of cholinergic parasympathetic-induced bronchoconstriction. Pilocarpine, a direct-acting cholinergic agonist (parasympathomimetic), is a selective stimulant of M_2 receptors.¹⁶ Inhalation of pilocarpine blocks cholinergic reflex bronchoconstriction caused by sulfur dioxide in human subjects without asthma, verifying that M_2 receptor stimulation can block cholinergic bronchoconstriction.¹⁷

In subjects with asthma, pilocarpine does not inhibit bronchoconstriction. This suggests the possibility of M_2 receptor dysfunction in asthma, resulting in increased cholinergic bronchoconstriction. If M_2 receptors fail to provide their normal inhibition of Ach release and bronchial contraction, this may explain why blockade of β receptors can cause such severe bronchoconstriction in patients with asthma. The normal balance of Ach inhibition by M_2 receptors is lacking, and β blockade by such drugs as propranolol leaves Ach stimulation of airway smooth muscle unchecked.

M_3 Receptors. M_3 receptors are present on submucosal glands and airway smooth muscle and possibly on surface goblet cells.



• **Fig. 5.11** Location and effects of muscarinic receptor subtypes in the pulmonary system. Ach, Acetylcholine.

Stimulation of M_3 receptors causes bronchoconstriction of smooth muscle and exocytosis and glandular secretion from submucosal mucous glands. M_3 receptors may also be present on airway epithelial cells to increase ciliary beat. Antagonism of M_3 receptors is the basis for a class of bronchodilator agents: the anticholinergic bronchodilators (see Chapter 7).

Muscarinic Receptors on Blood Vessels

Muscarinic M_3 receptors are located on endothelial cells of both the bronchial and the pulmonary vasculature. Stimulation of M_3 receptors causes release of an endothelium-derived relaxant factor.¹⁸ This relaxant factor, which produces vasodilation and is mediated by an increase in intracellular cyclic guanosine monophosphate (cGMP), has been identified as nitric oxide (NO) or a very similar nitrosocompound.¹⁹

Nonadrenergic, Noncholinergic Inhibitory Nerves

KEY POINT

In addition to sympathetic and parasympathetic nerves in the lung, there is evidence of a *nonadrenergic, noncholinergic (NANC) system*. This system has inhibitory and excitatory branches.

There is evidence of a branch of nerves that are neither parasympathetic (cholinergic) nor sympathetic (adrenergic) and that can cause relaxation of airway smooth muscle. These nerves have been termed *nonadrenergic, noncholinergic (NANC) inhibitory nerves*.²⁰ They are also referred to as simply *nonadrenergic inhibitory nerves* because adrenergic activity relaxes airway smooth muscle, and this is an additional but nonadrenergic neural method of relaxing such smooth muscle. Evidence of NANC inhibitory nerves is based on the following type of experimentation. When parasympathetic (cholinergic) receptors are blocked with an antagonist, such as atropine, and sympathetic (adrenergic) receptors are also blocked with a β blocker, such as propranolol, electrical field stimulation of the lung produces relaxation of bronchial smooth muscle. Katzung²¹ provided a more detailed description and evidence of this methodology. Fig. 5.12 illustrates this inhibitory system that is neither adrenergic nor cholinergic and its possible

neurotransmitter substances. A nonadrenergic inhibitory nervous system found in the gastrointestinal tract is primarily responsible for the relaxation of peristalsis and the internal anal sphincter. In the gastrointestinal tract, this system develops in conjunction with the parasympathetic branch. Embryologically, the gastrointestinal and respiratory tracts share a common origin, and the separation of the trachea and gut occurs around the fourth or fifth week of gestation. This common origin adds plausibility to the presence of a nonadrenergic inhibitory system in the lungs similar to that in the gastrointestinal tract.

KEY POINT

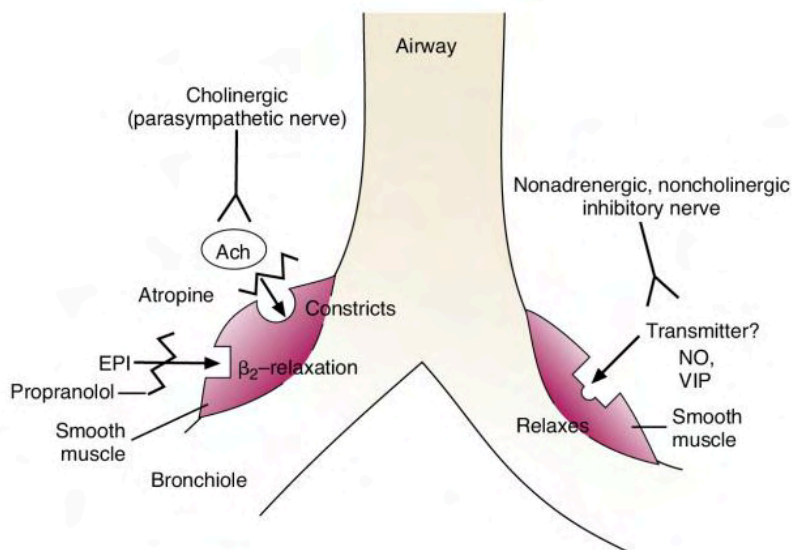
Inhibitory effects on airway smooth muscle cause bronchodilation and may be mediated by the neurotransmitter vasoactive intestinal peptide (VIP) or by nitric oxide (NO).

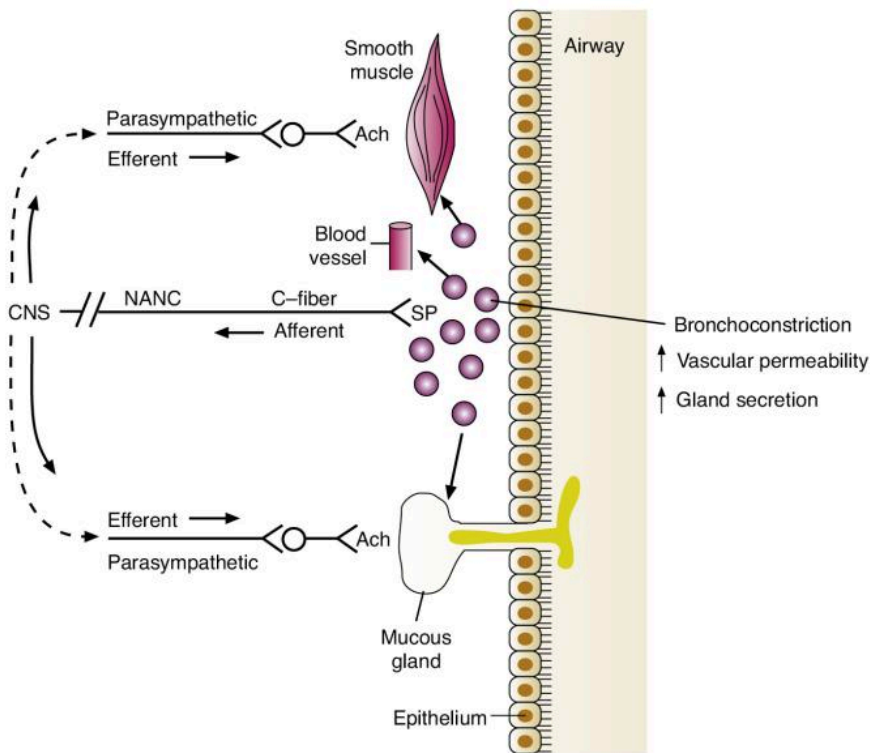
The exact neurotransmitter responsible for relaxation responses mediated by NANC inhibitory nerves is under investigation; however, the neurotransmitter vasoactive intestinal peptide (VIP) is the current front-runner.²² VIP can relax mammalian airway smooth muscle. Another possible neurotransmitter causing airway smooth muscle relaxation is NO. The enzyme responsible for NO synthesis, nitric oxide synthase (NOS), has been found in nerve terminals around airway smooth muscle, and NO produces effects similar to those caused by NANC inhibitory nerve activation. Ricciardolo²³ believed that NANC inhibition is mediated by NO with the help of VIP. An NANC inhibitory neurotransmitter substance has not yet been definitively identified.

Nonadrenergic, Noncholinergic Excitatory Nerves

The existence of *NANC excitatory nervous control* of airway smooth muscle has also been shown using electrical field stimulation (EFS) techniques. This system is also referred to as simply *noncholinergic excitatory nervous control* because cholinergic activity contracts airway smooth muscle, and this is an additional but noncholinergic neural method of exciting and constricting such smooth muscle. Stimulation of NANC excitatory nerves causes bronchial contraction. Sensory *afferent* nerves termed *C-fibers* are present in the airways, around bronchial blood vessels, around submucosal glands,

• **Fig. 5.12** Nonadrenergic inhibitory nervous system in the lung, which can cause relaxation of airway smooth muscle. Relaxation of smooth muscle occurs in the presence of cholinergic blockade by atropine and adrenergic blockade by propranolol. *Ach*, Acetylcholine; *EPI*, epinephrine; *NO*, nitric oxide; *VIP*, vasoactive intestinal peptide.





• **Fig. 5.13** Afferent C-fibers making up the nonadrenergic, noncholinergic (NANC) excitatory nervous system in the lung. Activation of C-fibers causes an afferent impulse with reflex parasympathetic activity and release of substance P, causing local effects in the airway. *Ach*, Acetylcholine; *CNS*, central nervous system; *SP*, substance P.

and within the airway epithelium. These afferent fibers follow the vagal nerve tracts into the CNS, as shown in Fig. 5.13.

KEY POINT

Excitatory effects, such as bronchoconstriction, are produced by afferent sensory fibers that have substance P as a neurotransmitter; these effects are caused by local release of substance P and by afferent–efferent reflex arcs involving efferent cholinergic transmission.

Sensory C-fiber nerves contain substance P, which is a tachykinin (a family of small peptide mediators). Substance P is also referred to as a *neuropeptide*. Sensory C-fibers can be stimulated by noxious substances, such as capsaicin, found in chili peppers. When stimulated, C-fibers conduct impulses to the CNS that result in reflexes of cough and parasympathetically induced bronchoconstriction. Sensory C-fibers also release their neuropeptides, such as substance P, at the local site of the nerve fiber. Substance P and other tachykinins cause bronchoconstriction in the airways and vasodilation, increased vascular permeability, mucous gland secretion, and enhanced mucociliary activity. The NANC excitatory C-fiber system has been considered a possible cause of the hyper-reactive airway seen in asthma. The presence of C-fibers is less marked in airways in humans than in rodent species.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Which portion of the nervous system is under voluntary control: the autonomic or the skeletal muscle motor nerve portion?

2. What is the neurotransmitter at each of the following sites: neuromuscular junction; autonomic ganglia; and most sympathetic end sites?
3. Where are muscarinic receptors found?
4. What is the effect of cholinergic stimulation on airway smooth muscle?
5. What is the effect of adrenergic stimulation on the heart?
6. Classify the drugs pilocarpine, physostigmine, propranolol, and epinephrine.
7. How do indirect-acting cholinergic agonists (parasympathomimetics) produce their action?
8. What effect would the drug atropine have on the eye and on airway smooth muscle?
9. What is the general difference between α and β receptors in the sympathetic nervous system?
10. What is the primary mechanism for terminating the neurotransmitters acetylcholine and norepinephrine?
11. What is the predominant sympathetic receptor type found on airway smooth muscle?
12. Identify the adrenergic receptor preference for phenylephrine, norepinephrine, and epinephrine.
13. What is the autoregulatory receptor on the sympathetic presynaptic neuron?
14. Classify the following drugs by autonomic class and receptor preference: dopamine, ephedrine, albuterol, phentolamine, propranolol, and prazosin.
15. What is the autoregulatory receptor on the parasympathetic presynaptic neuron at the terminal nerve site?
16. Contrast general α_1 -receptor and α_2 -receptor effects.
17. What substance may be the neurotransmitter in the NANC inhibitory nervous system in the lung?
18. What substance is the neurotransmitter in the NANC excitatory nervous system in the lung?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 42-year-old White woman with a long-standing history of asthma presents to the emergency department (ED) of a local acute care hospital. She states that she has been feeling as if her “heart was racing” today. She currently uses a β -adrenergic bronchodilator (albuterol) as needed and inhales an anticholinergic bronchodilator (ipratropium bromide) before bedtime; both drugs are administered by a metered dose inhaler (MDI).

On admission to the ED, she has the following vital signs: pulse (P) 155 beats/min, regular blood pressure (BP) 146/90 mm Hg, and respiratory rate (RR) 22 breaths/min with mild distress.

Her breath sounds are clear to auscultation, and a chest radiograph (posteroanterior [PA]) shows no abnormalities. Electrocardiography (ECG) lead II reveals supraventricular tachycardia (SVT). Oxygen saturation as revealed by pulse oximetry (peripheral capillary oxygen saturation [SpO_2]) is 90%. A resident orders oxygen at 2 L/min by nasal cannula and intravenous propranolol for SVT, which is given. Approximately 5 minutes later, her heart rate is reduced to 110 beats/min, but she begins to wheeze audibly and complains of severe shortness of breath (SOB), and her respiratory pattern is labored at 26 breaths/min. She is anxious, and her SpO_2 reading decreases from 92% to 72%.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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6

Adrenergic (Sympathomimetic) Bronchodilators

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Clinical Indications for Adrenergic Bronchodilators

- Indication for Short-Acting Agents
- Indication for Long-Acting Agents
- Indication for Racemic Epinephrine

Specific Adrenergic Agents and Formulations

- Catecholamines
 - Adrenergic Bronchodilators as Stereoisomers*
 - Keyhole Theory of β_2 Specificity*
 - Metabolism of Catecholamines*
- Resorcinol Agents
- Saligenin Agents

Levalbuterol: (R)-Isomer of Albuterol

Long-Acting β -Adrenergic Agents

Mechanism of Action

- β -Receptor and α_2 -Receptor Activation
- α_1 -Receptor Activation
- Long-Acting β Agonists: Mechanism of Action

Routes of Administration

- Inhalation Route
 - Continuous Nebulization*

Oral Route

Parenteral Route

Adverse Side Effects

- Tremor
- Cardiac Effects
- Tolerance to Bronchodilator Effect
- Loss of Bronchoprotection
- Central Nervous System Effects
- Fall in Arterial Oxygen Pressure
- Metabolic Disturbances
- Propellant Toxicity and Paradoxical Bronchospasm
- Sensitivity to Additives

Compatibility of Other Agents With Bronchodilators

β -Agonist Controversy

- Asthma Morbidity and Mortality

Respiratory Care Assessment of β -Agonist Therapy

- Before Treatment
- During Treatment and Short Term
- Long Term
 - For Long-Acting β Agonists*
- General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define sympathomimetic
2. Define *adrenergic*
3. List all currently available β -adrenergic agents used in respiratory therapy
4. Differentiate between the specific adrenergic agents and formulations
5. Describe the mechanism of action for each specific adrenergic agent and formulation
6. Describe the route of administration available for β agonists
7. Discuss adverse effects of β agonists
8. Clinically assess β -agonist therapy

KEY TERMS AND DEFINITIONS

Adrenergic bronchodilator Agent that stimulates sympathetic nervous fibers, which allow relaxation of smooth muscle in the airway. Also known as *sympathomimetic bronchodilator* or β_2 agonist.

α -Receptor stimulation Causes vasoconstriction and vasopressor effect; in the upper airway (nasal passages), this can provide decongestion.

Asthma paradox Refers to the increasing incidence of asthma morbidity, and especially asthma mortality, despite advances in the understanding of asthma and availability of improved drugs to treat asthma.

β_1 -Receptor stimulation Causes increased myocardial conductivity, heart rate, and contractile force.

β_2 -Receptor stimulation Causes relaxation of bronchial smooth muscle, with some inhibition of inflammatory mediator release and stimulation of mucociliary clearance.

Bronchospasm Narrowing of the bronchial airways caused by contraction of smooth muscle.

Catecholamines Group of similar compounds having sympathomimetic action; they mimic the actions of epinephrine.

Cyclic adenosine 3',5'-monophosphate (cAMP) Nucleotide produced by β_2 -receptor stimulation; it affects many cells but causes relaxation of bronchial smooth muscle.

Downregulation Long-term desensitization of β receptors to β_2 agonists caused by a reduction in the number of β receptors.

Sympathomimetic Producing effects similar to those of the sympathetic nervous system.

This chapter presents adrenergic drugs used as inhaled bronchodilators. The specific agents and the clinical indications for this class of drugs are summarized, along with their mechanism of action as mediated by β receptors. Structure–activity relationships of available agents are presented as a basis for their difference in receptor selectivity and duration of action. Differences among routes of administration are discussed, and side effects are reviewed. A brief summary of the debate over possible harmful effects with β agonists is given.

Clinical Indications for Adrenergic Bronchodilators

KEY POINT

The adrenergic bronchodilator group is used for the treatment of reversible airway obstruction in diseases, such as asthma and chronic obstructive pulmonary disease (COPD). These agents produce bronchodilation by stimulating β_2 receptors on airway smooth muscle.

The general indication for use of an **adrenergic bronchodilator** is relaxation of airway smooth muscle in the presence of reversible airflow obstruction associated with acute and chronic asthma (including exercise-induced asthma), bronchitis, emphysema, bronchiectasis, and other obstructive airway diseases. Differences in the rate of onset, peak effect, and duration led to a distinction between the uses of short-acting and long-acting agents. Various recommendations and guidelines exist for the use of β agonists in chronic obstructive pulmonary disease (COPD) and asthma.

CLINICAL CONNECTION

Short-acting β agonists (SABAs) are used to treat acute airflow obstruction, and these agents are often known as *rescue* and *reliever medications* in asthma and chronic obstructive pulmonary disease (COPD), respectively.

Indication for Short-Acting Agents

Short-acting β agonists, also known as SABAs, such as albuterol and levalbuterol, are indicated for relief of *acute* reversible airflow obstruction in asthma or other obstructive airway diseases, such as COPD.

CLINICAL CONNECTION

Long-acting β agonists (LABAs) are used to maintain airflow obstruction. Some LABAs have faster onset than SABAs, specifically formoterol, and have recommendations to use for asthma with an inhaled corticosteroid in patients older than 12 years of age.^{1,2} LABAs should never be used as monotherapy in treating acute bronchospasms.

Indication for Long-Acting Agents

Long-acting agents, such as salmeterol, formoterol, arformoterol, olodaterol, and vilanterol, are indicated for maintenance of bronchodilation and control of **bronchospasm** and nocturnal symptoms in asthma or other obstructive diseases, such as COPD. Salmeterol, formoterol, arformoterol, olodaterol, and vilanterol are long-acting β agonists (LABAs) or “controllers”; the slow time to peak effect makes long-acting agents poor rescue drugs. In asthma, a long-acting bronchodilator is usually combined with antiinflammatory medication for control of airway inflammation and bronchospasm. Although arformoterol, formoterol, olodaterol, and vilanterol have a rapid onset of action like or better than that of albuterol, their slower peak effect and prolonged activity make them better maintenance drugs than acute relievers or rescue agents. However, the use of formoterol paired with inhaled corticosteroids (ICS) is now a recommended for use in treating asthma in patients older than 12 years old.^{1,2}

CLINICAL CONNECTION

Racemic epinephrine should be used for its vasoconstricting effect to reduce upper airway swelling (i.e., croup, stridor) or to control bleeding in the airway. This agent should not be used to treat bronchoconstriction as it is not as effective as albuterol or levalbuterol.

Indication for Racemic Epinephrine

Racemic epinephrine is often used, either as an inhaled aerosol or via direct lung instillation, for its strong α -adrenergic vasoconstricting effect to reduce airway swelling after extubation; during epiglottitis and croup; and to control airway bleeding during endoscopy.

Specific Adrenergic Agents and Formulations

Table 6.1 lists adrenergic bronchodilators currently approved for general clinical use in the United States, as of the writing of this edition. Practitioners are urged to read package inserts on a drug before administration. These inserts give details of dosage strengths and frequencies, adverse effects, shelf life, and storage requirements, all of which are needed for safe application. Table 6.1 is not intended to replace more detailed information supplied by the manufacturer on each of the bronchodilator agents. There are three subgroups of adrenergic bronchodilators based on distinct differences in duration of action:

- *Ultrashort acting* (duration less than 3 hours): Racemic epinephrine
- *Short acting* (duration 4–6 hours): Albuterol and levalbuterol
- *Long acting* (duration 12–24 hours): Salmeterol, formoterol, arformoterol, olodaterol, and vilanterol

Catecholamines

The sympathomimetic bronchodilators are all either catecholamines or derivatives of catecholamines. A **catecholamine** is a chemical structure consisting of an aromatic catechol nucleus and a dialiphatic amine side chain. Fig. 6.1 shows the basic catecholamine structure, which is composed of a benzene ring with hydroxyl groups at the third and fourth carbon sites and an amine side chain attached at the first carbon position.

The terminal amine group (NH_2) and the benzene ring are connected by two carbon atoms, designated as α and β , a notation not to be confused with α and β receptors in the sympathetic nervous system. Examples of catecholamines are dopamine, epinephrine, norepinephrine, and isoproterenol. The first three occur naturally in the body. Catecholamines, or **sympathomimetic** amines, mimic the actions of epinephrine more or less precisely, causing tachycardia, elevated blood pressure, smooth muscle relaxation of bronchioles and skeletal muscle blood vessels,

TABLE 6.1 Inhaled Adrenergic Bronchodilator Agents Currently Available in the United States

Drug	Brand Name	Receptor Preference	Adult Dosage	Time Course (Onset, Peak, Duration)
Ultra-Short-Acting Adrenergic Bronchodilator Agents				
Epinephrine	Primatene Mist	α , β	MDI: 0.125 mg/puff, 1–2 puffs q4h, no more than 8 in 24h	Onset: 3–5 min Peak: 5–20 min Duration: 0.5–2 hr
Racemic epinephrine	Asthmanefrin	α , β	SVN: 2.25% solution, 0.25–0.5 mL (5.63–11.25 mg) qid	Onset: 3–5 min Peak: 5–20 min Duration: 0.5–2 hr
Short-Acting Adrenergic Bronchodilator Agents				
Albuterol	Proventil HFA, Ventolin HFA, ProAir HFA, ProAir Respiclick/Digihaler	β_2	SVN: 0.5% solution, 0.5 mL (2.5 mg), 0.63 mg, 1.25-mg and 2.5-mg unit dose, tid, qid MDI: 90 mcg/puff, 2 puffs tid, qid Tab: 2 mg, and 4 mg, tid, qid DPI: 108 mcg/puff, 2 puffs, tid, qid Syrup: 2 mg/5 mL, 1–2 tsp tid, qid	Onset: 15 min Peak: 30–60 min Duration: 5–12 hr
Levalbuterol	Xopenex, Xopenex HFA	β_2	SVN: 0.31 mg/3 mL tid, 0.63 mg/3 mL tid, or 1.25 mg/3 mL tid; concentrate 1.25 mg/0.5 mL, tid MDI: 45 mcg/puff, 2 puffs q4–6h	Onset: 15 min Peak: 30–60 min Duration: 5–8 hr
Long-Acting Adrenergic Bronchodilator Agents				
Salmeterol	Serevent Diskus	β_2	DPI: 50 mcg/blister bid	Onset: 20 min Peak: 3–5 hr Duration: 12 hr
Formoterol	Perforomist	β_2	SVN: 20 mcg/2-mL unit dose, bid	Onset: 15 min Peak: 30–60 min Duration: 12 hr
Arformoterol	Brovana	β_2	SVN: 15 mcg/2-mL unit dose, bid	Onset: 15 min Peak: 30–60 min Duration: 12 hr
Olodaterol	Stiverdi Respimat	β_2	SMI: 2.5 mcg/actuation, 2 actuations daily	Onset: 5 min Peak: 30–60 min Duration: 24 hr

DPI, dry powder inhaler; MDI, metered dose inhaler; SMI, soft-mist inhaler; qid, four times daily; SVN, small volume nebulizer; tid, Three times daily.

glycogenolysis, skeletal muscle tremor, and central nervous system (CNS) stimulation.

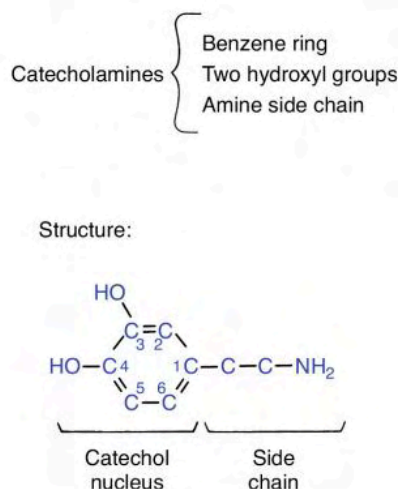
Adrenergic Bronchodilators as Stereoisomers

Adrenergic bronchodilators can exist in two different spatial arrangements, producing isomers. Rotation around the β carbon on the ethylamine side chain of the basic molecular structure, as seen in Fig. 6.1, produces two nonsuperimposable mirror images, termed *enantiomers* or simply *isomers*. Fig. 6.2 illustrates epinephrine as a *stereoisomer*, showing the (R)-isomers and (S)-isomers as the mirror image of each other. Enantiomers have similar physical and chemical properties but different physiologic effects. The (R)-isomer, or levo isomer, is active on airway β receptors, producing bronchodilation, and on extrapulmonary adrenergic receptors. The (S)-isomer, or dextro isomer, is not active on adrenergic receptors, such as β receptors, and until more recently the (S)-isomer was considered physiologically inert. The two mirror images of the isomers rotate light in opposite directions (see Fig. 6.2), providing two isomers, and this is the basis for designating them as dextrorotatory (*d*, +) or levorotatory (*l*, -). Using their actual spatial configuration, the levo isomer and dextro isomer are referred to as the (R)-isomer (for *rectus*, right) and (S)-isomer (for *sinister*, left), respectively. Adrenergic bronchodilators, such as epinephrine, albuterol, and salmeterol, have been produced synthetically as racemic mixtures, or 50:50 equimolar mixes of the (R)-isomers and (S)-isomers. Natural epinephrine found in the adrenal gland occurs as the (R)-isomer, or levo isomer, only. Lev-albuterol, released to the market in 1999, represents the first *synthetic* inhaled solution available as the single (R)-isomer of racemic

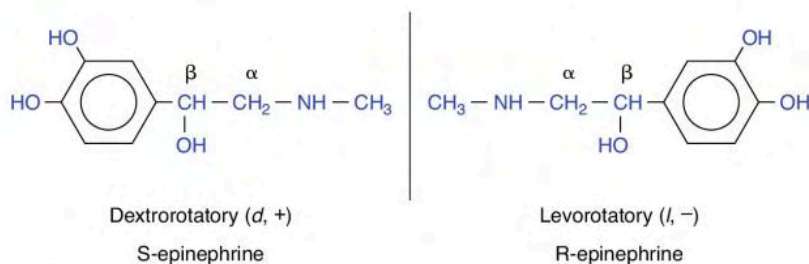
albuterol. Other bronchodilators, such as formoterol, have two or double stereogenic atoms on each side because it is a racemic mixture (50:50). Formoterol will have an RR isomer and an SS isomer; however, arformoterol, the single isomer of formoterol, will only have the RR isomer. Structures of the currently available inhaled β agonists to be discussed are shown in Fig. 6.3. Only a single isomer form is shown, for simplification and clarity.

Epinephrine. Epinephrine is a potent catecholamine bronchodilator that stimulates α and β receptors. Because epinephrine lacks β_2 -receptor specificity, there is a high prevalence of side effects, such as tachycardia, blood pressure increase, tremor, headache, and insomnia. Epinephrine occurs naturally in the adrenal medulla and has a rapid onset but a short duration because of metabolism by catechol *O*-methyltransferase (COMT). It has been administered both via inhalation and subcutaneous injection to treat patients with asthma exacerbation. It is also used as a cardiac stimulant, on the basis of its strong β_1 effects. Self-administered, intramuscular injectable doses of 0.3 mg and 0.15 mg are marketed to control systemic hypersensitivity (anaphylactic) reactions.

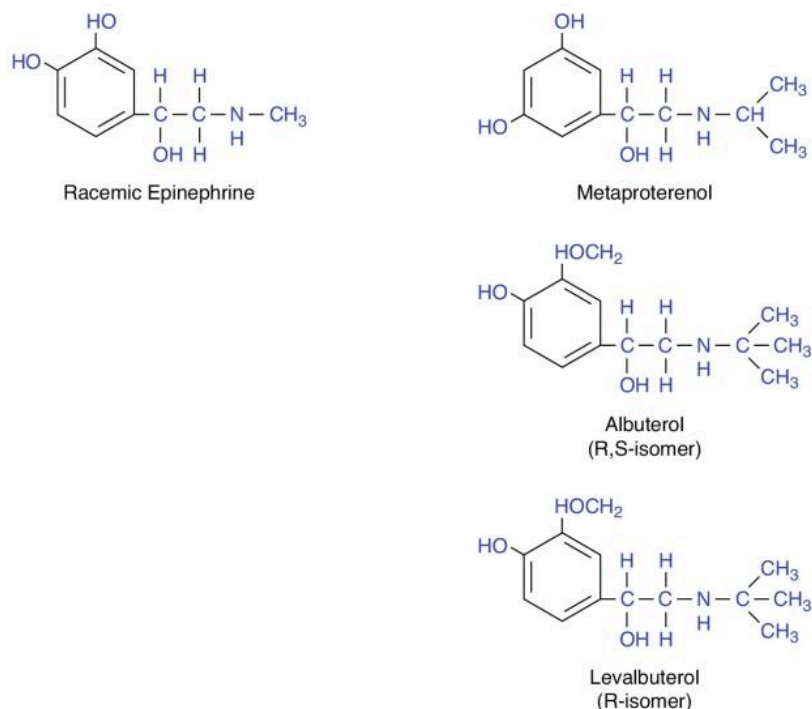
This drug is more useful for the management of acute asthma rather than for daily maintenance therapy because of its pharmacokinetics and side effect profile; however, there are better β_2 agonists for the treatment of acute asthma. The parenteral form of epinephrine is a natural extract, consisting of only the (R)-isomer, or levo isomer. The synthetic formulation of epinephrine for nebulization, Asthmanefrin, is a racemic mixture of the (R)-isomer, or levo isomer, and (S)-isomer, or dextro isomer. The mechanism of action of racemic epinephrine is the same as with natural epinephrine, giving α and β stimulation. Because only the (R)-isomer is active on adrenergic receptors, a 1:100 strength formulation of natural epinephrine (injectable formulation) has been used for nebulization, whereas a 2.25% strength racemic mixture is used in nebulization. An epinephrine metered dose inhaler (MDI) was sold over the counter (OTC) as Primatene Mist. The US Food and Drug Administration (FDA) ruled in 2006 that Primatene Mist was not essential, which led to its removal from the market on December 31, 2011.³ However, Nephron Pharmaceuticals launched Asthmanefrin (racemic epinephrine) as an OTC product in 2012. Asthmanefrin is available as a liquid nebulizer solution and is powered by a battery-operated atomizer. Other OTC products using epinephrine as the base have been found on the Internet. Epi Mist uses racemic epinephrine in conjunction with a bulb atomizer, and Prime Asthma Relief is a dry power inhaler (DPI) of racemic epinephrine. All these OTC products have received admonitions from the FDA for product issues or misinformation; however, the FDA does not regulate OTC medications. Additionally, Amphastar Pharmaceuticals purchased the name Primatene Mist in 2008, starting the conversion to a hydrofluoroalkane (HFA) MDI containing epinephrine. In 2018, Amphastar



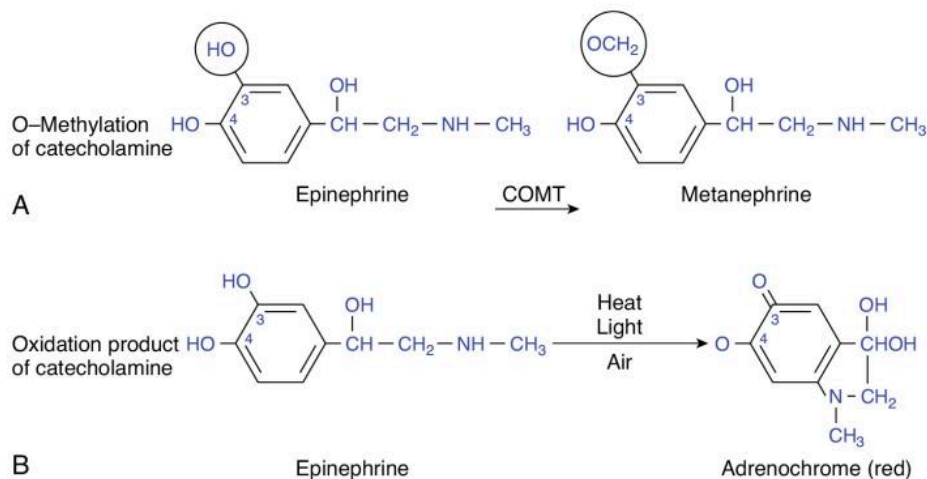
• **Fig. 6.1** Basic catecholamine structure, showing the catechol nucleus connected to an amine side chain.



• **Fig. 6.2** Structure of epinephrine, illustrating the (R)-isomer (levo, *l*, -) and (S)-isomer (dextro, *d*, +) as mirror images of each other, termed *enantiomers*. Natural epinephrine is (R)-epinephrine. Synthetic formulations for inhalation are racemic (50:50) mixtures of (R)-isomers and (S)-isomers.



• **Fig. 6.3** Chemical structures of short-acting inhaled adrenergic bronchodilators currently available in the United States. With the exception of natural epinephrine and levalbuterol, all formulations are racemic mixtures and are shown in the same orientation for clarity. The isomers of racemic albuterol and levalbuterol are labeled to indicate the difference between these two drugs. Long-acting agents are illustrated in Fig. 6.8. (From Rau, J. L. [2000]. Inhaled adrenergic bronchodilators: historical development and clinical application. *Respiratory Care*, 45, 854.)



• **Fig. 6.4** **A**, Inactivation of the catecholamine epinephrine by the enzyme catechol O-methyltransferase (COMT). **B**, Conversion of a catecholamine such as epinephrine to an adrenochrome.

Pharmaceuticals filed a NDA with the FDA and Primatene Mist was approved in 2019 as an HFA MDI of epinephrine.⁴

Keyhole Theory of β_2 Specificity

The theory that explains the shift from α activity to β_2 specificity has been termed the *keyhole theory* of β sympathomimetic receptors: The larger the side chain attachment to a catechol base, the greater is the β_2 specificity. If the catecholamine structural pattern is understood as a keylike shape, then the larger the “key” (side chain), the more β_2 specific is the drug. The increase in side chain substitutions can be seen in the drug structures presented in Fig. 6.3 for the three catecholamines described above and for the β_2 -selective agents to be discussed in later sections.

Metabolism of Catecholamines

Despite the increase in β_2 specificity with increased side chain bulk, all of the previously mentioned catecholamines are rapidly

inactivated by the cytoplasmic enzyme COMT. This enzyme is found in the liver and kidneys and throughout the rest of the body. Fig. 6.4, *A* illustrates the action of COMT as it transfers a methyl group to the carbon-3 position on the catechol nucleus. The resulting compound, metanephrine, is inactive on adrenergic receptors. Because the action of COMT on circulating catecholamines is very efficient, the duration of action of these drugs is severely limited, with a range of 1.5 to at most 3 hours.

Catecholamines are also unsuitable for oral administration because they are inactivated in the gut and liver by conjugation with sulfate or glucuronide at the carbon-4 site. Because of this action, they have no effect when taken by mouth, limiting their route of administration to inhalation or injection. Catecholamines are also readily inactivated to inert adrenochromes by heat, light, or air (see Fig. 6.4, *B*). For this reason, racemic epinephrine is stored in an amber-colored bottle or a foil-protected wrapper. Nebulizer *rainout* (i.e., nebulized particles that condense and fall,

under the influence of gravity) in the tubing may appear pinkish after treatment, and a patient's sputum may even appear pink tinged after using aerosols of catecholamines.

Resorcinol Agents

KEY POINT

The basic catecholamine structure, consisting of a catechol ring connected to an amine side chain, directly influences activity. β_2 -receptor specificity is caused by side chain bulk (*keyhole theory*). The short duration of action of catecholamines results from metabolism by the enzyme catechol *O*-methyltransferase (COMT).

Because the limited duration of action with catecholamines is unsuitable for maintenance therapy of bronchospastic airways, drug researchers sought to modify the catechol nucleus, which is highly vulnerable to inactivation by COMT. As a result, the hydroxyl attachment at the carbon-4 site was shifted to the carbon-5 position, producing a resorcinol nucleus (see Fig. 6.3). This change resulted in *metaproterenol* (named for the 3',5'-attachments in the meta position). Because metaproterenol is not inactivated by COMT, it has a significantly longer duration of action of 4 to 6 hours compared with the short-acting catecholamine bronchodilators. Metaproterenol can be taken orally because it resists inactivation by sulfatase enzymes in the gastrointestinal tract and in the liver. For these reasons, newer generations of resorcinols and other catecholamine derivatives are much better suited for maintenance therapy compared with the older catecholamine agents. Metaproterenol is slower to reach a peak effect (30–60 minutes) than racemic epinephrine. The MDI chlorofluorocarbon (CFC) version of metaproterenol was removed from the market on June 14, 2010.

KEY POINT

Modification of the catecholamine structure produces *noncatecholamines*, such as albuterol and levalbuterol, which have a 4- to 6-hour duration when inhaled and are β_2 preferential.

Saligenin Agents

A different modification of the catechol nucleus at the carbon-3 site resulted in the saligenin *albuterol*, referred to as *salbutamol* in Europe (see Fig. 6.3). Albuterol is available in various pharmaceutical vehicles in the United States, including oral extended-release tablets, syrup, nebulizer solution, and MDI. As with the resorcinol bronchodilators, this drug has a β_2 -preferential effect; it is also effective via oral administration. Inhaled albuterol has a duration of approximately 4 to 6 hours, with a peak effect in 30 to 60 minutes. However, duration of up to 12 hours can be achieved

with oral dosing from extended-release tablets. Oral use may lead to greater systemic side effects than its inhaled counterpart.

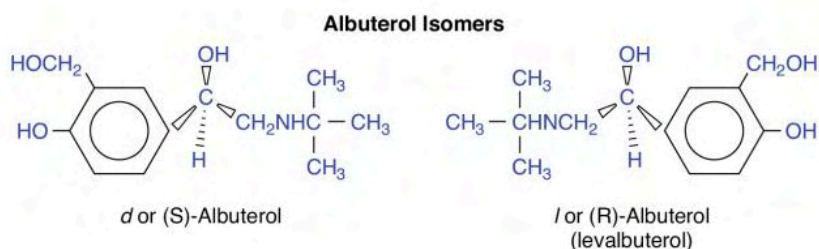
Levalbuterol: (R)-Isomer of Albuterol

Previous inhaled formulations of adrenergic bronchodilators were all synthetic racemic mixtures, containing the (R)-isomer and the (S)-isomer in equal amounts. Levalbuterol is the pure (R)-isomer of racemic albuterol. Both stereoisomers of albuterol are shown in Fig. 6.5. Although the (S)-isomer is physiologically inactive on adrenergic receptors, there is accumulating evidence that the (S)-isomer is *not* completely inactive. Barnes⁵ suggested, however, there is no difference between single isomer levalbuterol and racemic albuterol. Box 6.1 lists some of the physiologic effects of (S)-isomer of albuterol noted in the literature.^{6–12} The effects noted would antagonize the bronchodilating effects of the (R)-isomer of an adrenergic drug and promote bronchoconstriction. In addition, the (S)-isomer is more slowly metabolized than the (R)-isomer. Levalbuterol is the single (R)-isomer form of racemic albuterol and is available in an HFA-propelled MDI, with nebulization solution in three strengths: 0.31-mg, 0.63-mg, and 1.25-mg unit doses. Levalbuterol is also available as a concentrate of 1.25 mg in 0.5 mL. In a study by Nelson et al.,¹³ the 0.63-mg dose was found to be comparable with the 2.5-mg racemic albuterol dose in onset and duration (Fig. 6.6).

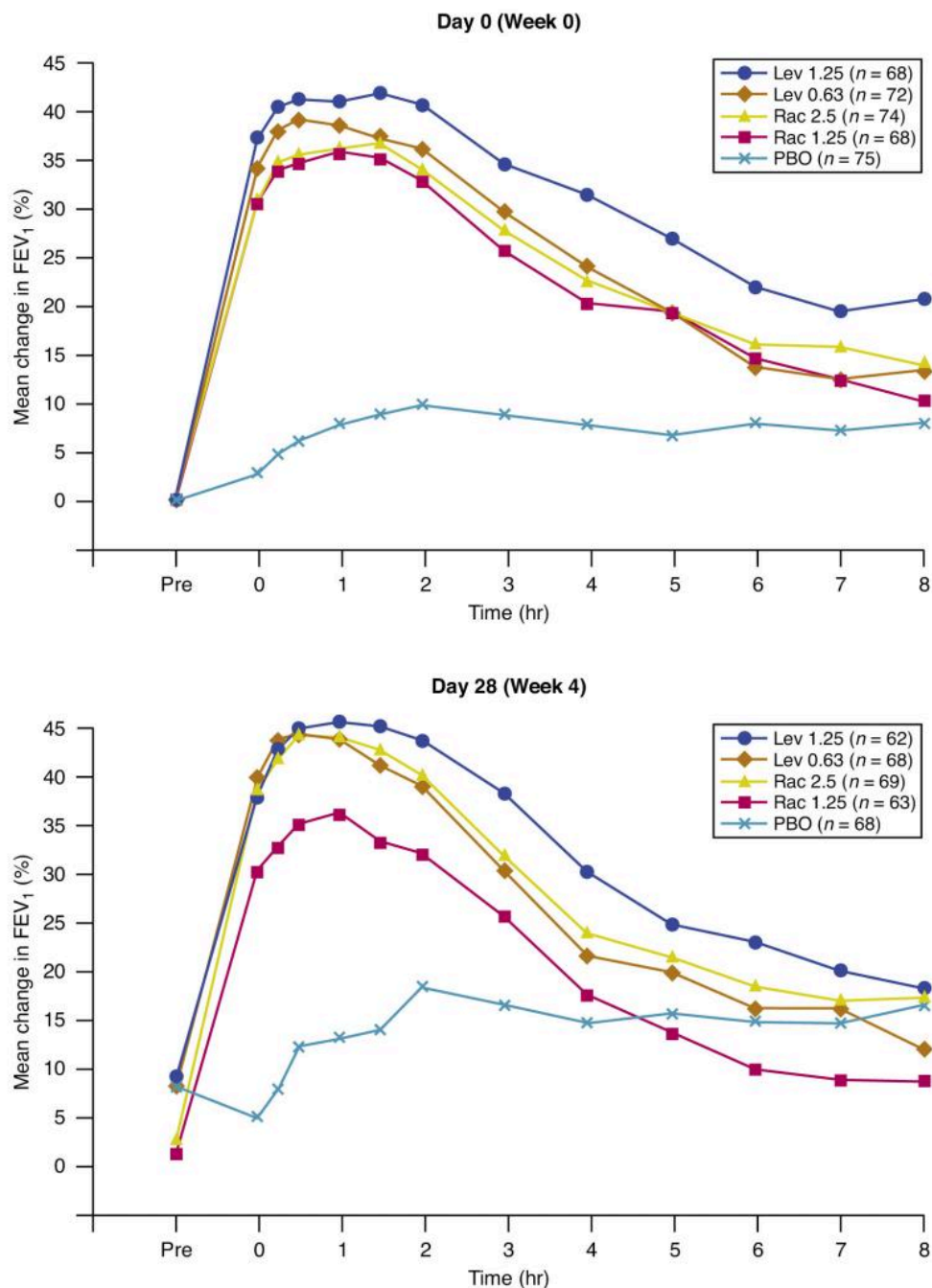
Side effects, such as tremor and heart rate changes, were fewer with the single-isomer formulation. The 1.25-mg levalbuterol dose showed a higher peak effect on forced expiratory volume in 1 second (FEV₁) with an 8-hour duration compared with racemic albuterol. Side effects with this dose were equivalent to the side effects seen with racemic albuterol. It is significant that an equivalent clinical response was seen with one fourth the racemic dose (0.63 mg) when using the pure isomer, although the racemic mixture contains 1.25 mg of the (R)-isomer (one half of the total 2.5-mg dose).

• BOX 6.1 Effects and Characteristics of the (S)-Isomer of Albuterol

- Increases intracellular calcium concentration *in vitro*⁸
- Activity is blocked by anticholinergic agent atropine³
- Does not produce pulmonary or extrapulmonary β_2 -mediated effects⁹
- Enhances experimental airway responsiveness *in vitro*¹⁰
- Increases contractile response of bronchial tissue to histamine or leukotriene C₄ (LTC₄) *in vitro*¹¹
- Enhances eosinophil superoxide production with interleukin-5 (IL-5) stimulation¹²
- Is metabolized slower than (R)-albuterol *in vivo*³
- Preferentially retained in the lung when inhaled by metered dose inhaler (*in vivo*)¹



• **Fig. 6.5** The (R)-isomer and (S)-isomer of racemic albuterol. Levalbuterol is the single, (R)-isomer form of racemic albuterol and contains no (S)-isomer.



• **Fig. 6.6** Mean percent change in forced expiratory volume in 1 second (FEV_1) from baseline (week 0) to the end of treatment (week 4) with various doses of levalbuterol (*Lev*), racemic albuterol (*Rac*), and a placebo (*PBO*). (From Nelson, H. S., Bensch, G., Pleskow, W. W., et al. [1998]. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *Journal of Allergy and Clinical Immunology*, 102, 943.)

Long-Acting β -Adrenergic Agents

The trend in adrenergic bronchodilators has been toward development from nonspecific, short-acting agents, such as epinephrine, to β_2 -specific agents with action lasting 4 to 6 hours, such as albuterol and levalbuterol. Longer-acting agents offer the advantages of less frequent dosing and protection through the night for

patients with asthma. These agents include salmeterol (Serevent), formoterol (Perforomist), arformoterol (Brovana), and olodaterol (Striverdi Respimat). Long-acting broncho dilators are contrasted with short-acting agents. Short-acting agents include albuterol and levalbuterol, although these agents at one time were considered longer acting compared with the ultra-short-acting catecholamines, such as racemic epinephrine.

KEY POINT

Salmeterol, formoterol, arformoterol, and olodaterol are long-acting β_2 agonists with a 12- to 24-hour duration of action resulting from their unique pharmacodynamics (drug–receptor interaction).

Extended-Release Albuterol

An extended-release form of albuterol (VoSpire ER) is no longer available. This was a 4-mg or 8-mg tablet taken orally with extended activity up to 12 hours. At this time, no generic extended-release albuterol is available.

Salmeterol

Salmeterol, a β_2 -selective receptor agonist, is available in a dry powder formulation in the Diskus inhaler. Salmeterol xinafoate is a racemic mixture of two enantiomers, with the (R)-isomer containing the predominant β_2 activity.¹⁴

Bronchodilator Effect. Salmeterol represents a new generation of long-acting β_2 -specific bronchodilating agents, whose bronchodilation profile differs from the agents previously discussed. The median time to reach a 15% increase in FEV₁ above the baseline (considered the onset of bronchodilation) in subjects with asthma is longer with salmeterol than with albuterol; it has been reported to be approximately 15 minutes.¹⁵ The slower onset of action with salmeterol is significant for its clinical application (discussed subsequently). The time to peak bronchodilating effect is generally 3 to 5 hours, and its duration of action in maintaining an FEV₁ 15% above the pretreatment baseline is 12 hours or longer. At each point (onset, peak effect, and duration), salmeterol exhibits slower, longer times for effect compared with shorter-acting bronchodilators, such as albuterol.

With inhaled salmeterol xinafoate, an initial peak plasma concentration of 1 to 2 mcg/L is seen 5 minutes after inhalation, with a second peak of 0.07 to 0.2 mcg/L at 45 minutes; the second peak is probably caused by absorption of the swallowed dose. The drug is metabolized by hydroxylation, with elimination primarily in feces.¹⁴ The increased duration of action of salmeterol results from the increased lipophilicity conferred by the long side chain. The “tail” of the molecule anchors at an exosite in the cell membrane and allows continual activation of the β receptor. The mechanism of action is discussed more fully subsequently.

Formoterol

Formoterol is another β_2 -selective agonist with a long-acting bronchodilatory effect of 12 hours in duration. Foradil, a racemic mixture of (R,R)-formoterol and (S,S)-formoterol, was approved by the FDA for maintenance treatment of asthma and for acute prevention of exercise-induced bronchospasm in adults and in children 5 years of age or older. Formoterol is also indicated for the treatment of COPD and can be used in conjunction with other inhaled medications, such as inhaled corticosteroids, short-acting β agonists, and theophylline. Formoterol (Perforomist) is available as a generic.

The use of liquid nebulization is still very popular with many patients and is a great alternative to MDI and DPI use. Perforomist is available in a liquid nebulization form of 20 mcg/2 mL unit dose and is prescribed twice daily. Currently, it is approved only for use with COPD.

The chemical structure of formoterol is shown in Fig. 6.7. As with salmeterol, the extensive side chain, or “tail,” makes formoterol more lipophilic than the shorter-acting

bronchodilators and is the basis for its longer duration of effect. The increased lipophilicity of salmeterol and formoterol allows the drugs to remain in the lipid cell membrane. Even if a tissue preparation containing the drugs is perfused or washed, the drug activity persists. Salmeterol is more lipophilic than formoterol, and this along with its anchoring capability may explain why salmeterol is less prone to being “washed away” compared with formoterol.¹⁵

Bronchodilator Effect. Similar to salmeterol, formoterol has a prolonged duration of bronchodilating effect of up to 12 hours. In contrast to salmeterol, the onset of action for formoterol is significantly faster. The time from inhalation to significant bronchodilation is similar to that of albuterol. It has been reported that 1 minute after inhalation of formoterol, there is a significant increase in specific airway conductance (SG_{AW}).¹⁶ The onset of bronchodilation is generally considered to take 2 to 3 minutes with formoterol compared with 10 minutes or longer with salmeterol. Fig. 6.8 shows the dose-proportional response to inhaled (R,R)-formoterol, the single isomer isolated from the racemic mixture of (R,R)-formoterol and (S,S)-formoterol, compared with inhaled racemic albuterol.¹⁷ A study¹⁸ compared racemic formoterol, 24 mcg; salmeterol, 50 mcg; and albuterol, 200 mcg. They found that the increases in SG_{AW} after 1 minute were 44%, less than 16%, and 44%, respectively; the times to maximal increase in airway conductance were 2 hours, 2 to 4 hours, and 30 minutes, respectively; and the maximal increases were 135%, 111%, and 100%, respectively.^{16,18}

The efficacy of formoterol in relaxing airway smooth muscle—its maximal effect—is greater than that of albuterol, which, in turn, is greater than that of salmeterol. The lower intrinsic efficacy of salmeterol would make it a better agent than formoterol for patients with cardiovascular disease.¹⁴

Arformoterol

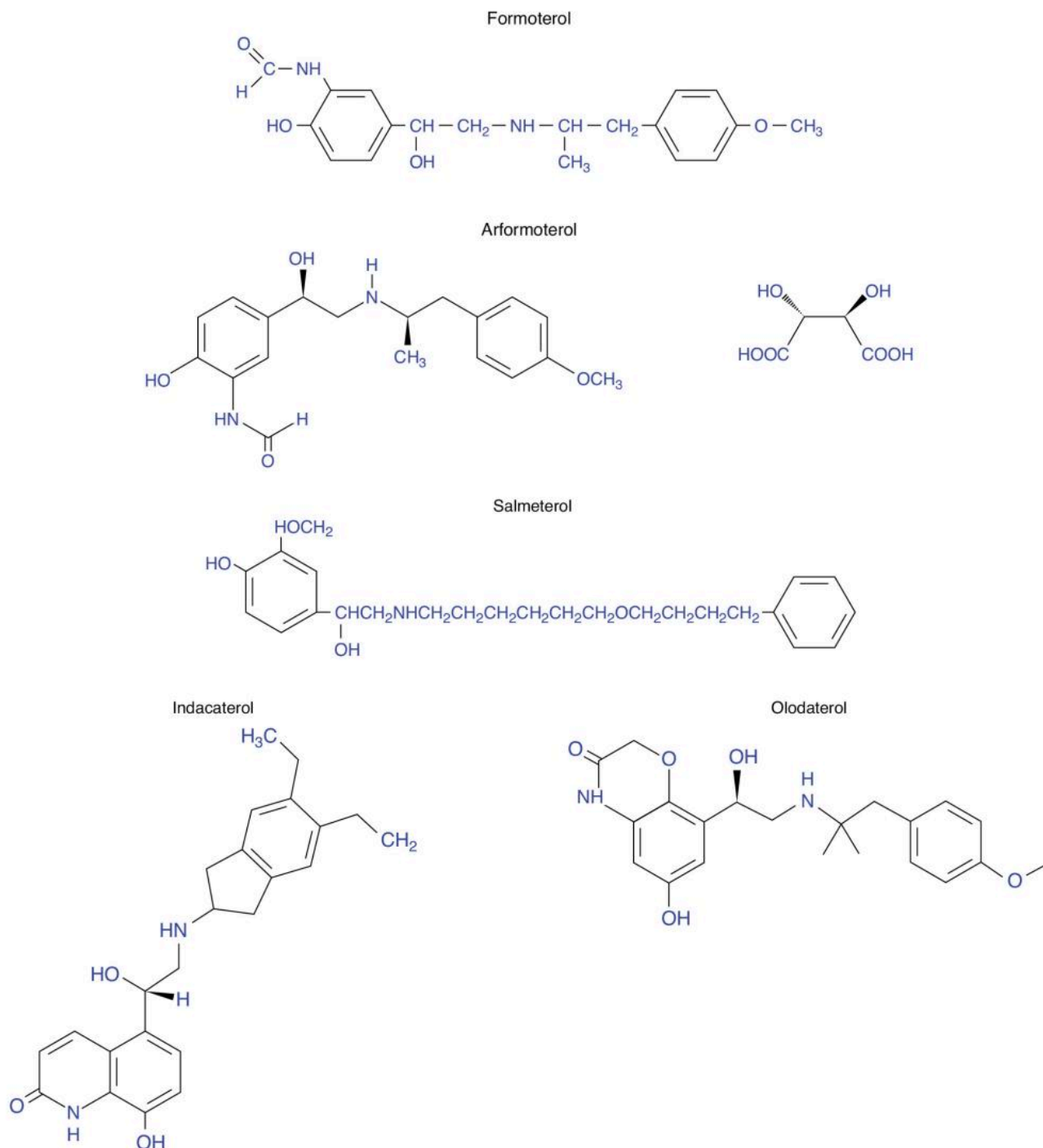
Arformoterol is a β_2 -selective agonist with a long-acting bronchodilatory effect of 12 hours in duration. Arformoterol (Brovana) is the single, (R,R)-isomer form of racemic formoterol, which is approved by the FDA for maintenance treatment of COPD. The current recommended adult dose is 15 mcg twice daily. Brovana is available in 2-mL unit-dose vials and is indicated for nebulization only. Arformoterol is available as a generic.

Indacaterol

Sunovion, the manufacturer of Brovana, was the marketer of Arcapta Neohaler (indacaterol) but discontinued its production in the US in March 2020.¹⁹ Currently, indacaterol is not utilized in any other fixed drug combination in the US, as Utibron (indacaterol/glycopyrrolate) Neohaler, and Seebri (glycopyrrolate) Neohaler have been discontinued. However, other studies demonstrate that indacaterol/glycopyrrolate/mometasone is being studied for asthma with good results.²⁰

Olodaterol

Olodaterol (Striverdi Respimat) is an ultra-long-acting β agonist approved by the FDA in 2014. The dose is 5 mcg once daily via Respimat for treatment of COPD. Olodaterol has a quick onset, similar to formoterol. The change in FEV₁ is seen in approximately 5 minutes.²¹ Olodaterol has been observed to exhibit 24-hour duration of effect in patients with COPD.²² Currently,



• **Fig. 6.7** Chemical structures of formoterol, arformoterol, salmeterol, and olodaterol, long-acting β_2 agonists (LABAs).

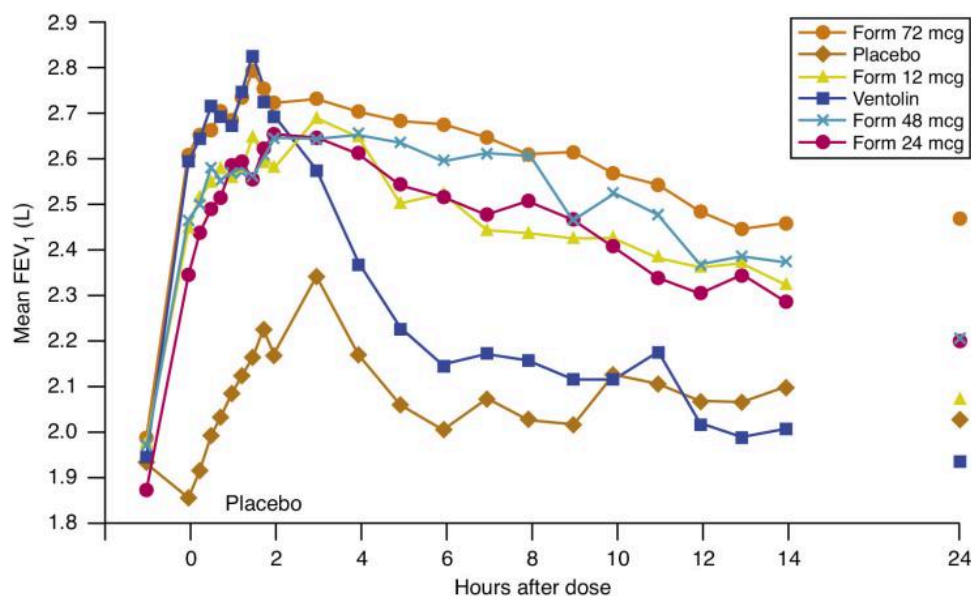
olodaterol is not FDA approved for asthma; however, it has been shown to be effective as monotherapy as well as in combination with tiotropium in animal studies.²³

CLINICAL CONNECTION

Vilanterol is not available as monotherapy and is currently found in fixed drug combinations only.

Vilanterol

Vilanterol is an ultra-long-acting β agonist that is FDA approved in fixed combination agents with fluticasone (Breo Ellipta), umeclidinium (Anoro Ellipta), and fluticasone and umeclidinium (Trellagy Ellipta). Vilanterol has been studied as monotherapy with effective results in patients with COPD.²⁴ At the time of writing, vilanterol is not available as monotherapy; it is only found in fixed combinations.



• **Fig. 6.8** Single-dose crossover study of (*R,R*)-formoterol in the treatment of asthmatic adults. Shown are the dose-proportional forced expiratory volume in 1 second (FEV_1) responses and duration of action for the single isomer (*R,R*)-formoterol, a long-acting β_2 agonist (LABA).

Antiinflammatory Effects

Both the SABAs and LABAs show antiinflammatory effects in vitro. β agonists inhibit human mast cell activation and degranulation in vitro, prevent increase in vascular permeability with inflammatory mediators, and generally diminish the attraction and accumulation of airway inflammatory cells.^{15,20–24} Despite these in vitro antiinflammatory effects, they have not been shown to inhibit the accumulation of inflammatory cells in the airway or the increase in inflammatory markers in vivo. Neither drug is considered to have a sufficient effect on airway inflammation in patients with asthma to replace antiinflammatory drugs, such as corticosteroids.

Clinical Use

LABAs are indicated for maintenance therapy of asthma that is not controlled by regular low-dose inhaled corticosteroids and for COPD needing daily inhaled bronchodilator therapy for reversible airway obstruction. National guidelines recommend the introduction of an LABA in step 3 care of asthma (asthma not controlled by lower doses of antiinflammatory medications)¹ and use as deemed necessary for COPD.²⁵ Use of LABAs may prevent the need to increase the inhaled dose of corticosteroid. Several points should be noted in the clinical use of long-acting agents because of their differences from SABAs.

- LABAs are not recommended for rescue bronchodilation because repeated administration with their longer duration and increased lipophilic property risk accumulation and toxicity.¹⁵
- An SABA, such as albuterol or other agents previously discussed, should be prescribed and available for asthmatics for treatment of breakthrough symptoms if additional bronchodilator therapy is needed between scheduled doses of an LABA; patients with asthma must be well educated in the appropriate use of the two types of β agonists (SABA versus LABA). New data suggests the use of formoterol/ICS as a reliever in place of a SABA.^{1,2}

- Although they have antiinflammatory effects, SABAs and LABAs are not a substitute for inhaled corticosteroids in asthma control or for other antiinflammatory medications, if such are required.
- The difference in rate of onset between salmeterol and formoterol, or olodaterol may require classifying β_2 agonists as “fast” and “slow” in addition to “short” and “long” acting, with salmeterol classified as a slow and long-acting bronchodilator versus formoterol as a fast and long-acting bronchodilator.²⁵ We may also see some agents, such as olodaterol, being classified as “ultra”-long-acting because of their 24-hour duration.

The addition of an LABA to inhaled corticosteroids can lead to improved lung function and a decrease in symptoms.^{24–27} A combination product of salmeterol and fluticasone in a Diskus inhaler (Advair Diskus) showed superior asthma control and better lung function compared with either drug taken alone.^{28–31} Because of their prolonged bronchodilation, LABAs taken twice daily have a greater area under the FEV_1 curve compared with short-acting agents taken four times daily. However, once-daily LABAs are demonstrating a better area under the curve (AUC) compared with those taken twice daily.^{19–24} In contrast to albuterol, which tends to return to baseline in 4 to 6 hours, salmeterol provides a more sustained level of bronchodilation, giving a higher baseline of lung function.^{32,33} The same effect has been found in comparing twice-daily salmeterol with four-times-daily inhaled ipratropium bromide,³³ a shorter-acting anticholinergic bronchodilator, which is discussed in Chapter 7.

Salpeter et al.,³⁴ in a meta-analysis, reported that LABAs increased the risk of asthma hospitalizations and deaths compared with a placebo. Nelson et al.³⁵ also described increased death rates among patients using salmeterol; their findings reported the highest death rate among African Americans. These studies did not consider the severity of asthma and whether the participants used other medications. Asthma may have been worse in some

participants than in others. With regard to cotreatments, the studies could not account for other medications that the participants may have been taking or with what regularity they were taking them. The latter could have serious consequences if, for example, a participant stopped using inhaled corticosteroids that were prescribed to treat asthma. Any of these variables—asthma severity, presence of cotreatments, and patient adherence—could affect interpretation of data. Nevertheless, the labeling of these agents has been changed to warn that death can occur.

Because of the ongoing concerns about the safety of LABAs, the FDA is now requiring changes on how LABAs are used in the treatment of asthma. As of June 2, 2010, the FDA now requires the following:

- LABAs are not to be used without a controller medication (i.e., corticosteroid).
- LABAs should not be used by patients whose asthma is controlled on low-dose or medium-dose inhaled corticosteroids.
- LABAs should be used only if the asthma is not controlled with such agents as inhaled corticosteroids.
- LABAs should be for short-term use only. Once asthma is controlled, the LABA should be discontinued.
- Children should use an LABA only in conjunction with a corticosteroid. The use of a combination product is needed to increase adherence.

Mechanism of Action

The bronchodilating action of the adrenergic drugs is caused by stimulation of β_2 receptors located on bronchial smooth muscle.

In addition to β_2 receptors, some adrenergic bronchodilators can stimulate α and β_1 receptors, with the following clinical effects:

- **α -Receptor stimulation:** Causes vasoconstriction (i.e., a *vaso-pressor* effect); in the upper airway (nasal passages), this can provide decongestion
- **β_1 -Receptor stimulation:** Causes increased myocardial conductivity, heart rate, and contractile force
- **β_2 -Receptor stimulation:** Causes relaxation of bronchial smooth muscle, with some inhibition of inflammatory mediator release and stimulation of mucociliary clearance

Both α and β receptors are examples of G protein–linked receptors. Table 6.2 includes each of the adrenergic receptor types, along with its particular type of G protein, effector system, second messenger, and an example of cell response in the lungs. As described in Chapter 2, the G protein is a heterotrimer whose α subunit differentiates the type of G protein. The G protein couples the adrenergic receptor to the effector enzyme, which initiates the cell response by means of a particular intracellular second messenger. The mechanism of action with β -receptor, α_2 -receptor, and α_1 -receptor stimulation is described for each.

β -Receptor and α_2 -Receptor Activation

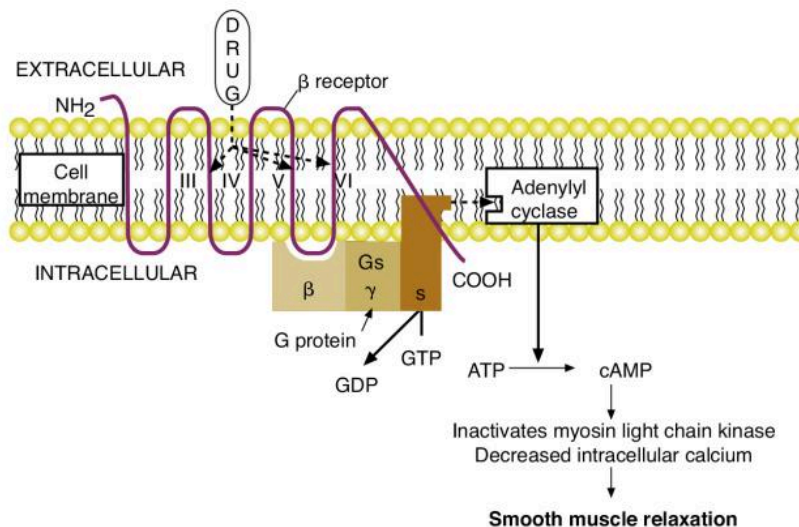
The mechanism of action of β agonists and the β receptors has been well characterized, although the activity of α receptors is not as well understood. The mechanism of action for relaxation of airway smooth muscle when a β_2 receptor is stimulated is illustrated in Fig. 6.9. Adrenergic agonists, such as albuterol or epinephrine,

TABLE 6.2 Adrenergic Receptor Types: G Proteins, Effector Systems, Second Messengers, and Examples of Cell Responses

Receptor	G Protein	Effector	Second Messenger	Response
α_1	G_q	Phospholipase C (PLC)	Inositol triphosphate (IP_3), diacylglycerol (DAG)	Vasoconstriction
α_2	G_i	Adenylyl cyclase (inhibits)	cAMP (inhibits)	Inhibition of neurotransmitter release
β ($\beta_1, \beta_2, \beta_3$)	G_s	Adenylyl cyclase (stimulates)	cAMP (increases)	Smooth muscle relaxation

cAMP, Cyclic adenosine 3',5'-monophosphate.

- **Fig. 6.9** Diagram illustrating mechanism of action by which stimulation of the G protein–linked β receptor by a β agonist causes smooth muscle relaxation. *ATP*, Adenosine triphosphate; *cAMP*, cyclic adenosine 3',5'-monophosphate; *COOH*, carboxy; *GDP*, guanosine diphosphate; *GTP*, guanosine triphosphate; *NH₂*, amine group.



attach to β receptors, which are polypeptide chains that traverse the cell membrane seven times and have an extracellular NH_2 terminus and an intracellular carboxy (COOH) terminus. This attachment causes activation of the stimulatory G protein, designated G_s . The actual binding site of a β agonist is within the cell membrane, inside the “barrel” or circle formed by the transmembrane loops of the receptor chain. The β agonist forms bonds with elements of the third, fifth, and sixth transmembrane loops. When stimulated by a β agonist, the receptor undergoes a conformational change that reduces the affinity of the α subunit of the G protein for guanosine diphosphate (GDP). The GDP is replaced by guanosine triphosphate (GTP), and the α subunit dissociates from the receptor and the β - γ portion of the G protein to link with the effector system. The effector system for the β receptor is adenylyl cyclase, a membrane-bound enzyme. Activation of adenylyl cyclase by the α subunit of the G_s protein causes increased synthesis of the second messenger, **cyclic adenosine 3',5'-monophosphate (cAMP)**. cAMP may cause smooth muscle relaxation by increasing the inactivation of myosin light chain kinase, an enzyme that initiates myosin-actin interaction and subsequent smooth muscle contraction. An increase in cAMP also leads to a decrease in intracellular calcium.

A similar sequence of events is responsible for the action of α_2 -receptor stimulation, which can inhibit further neurotransmitter release from the presynaptic neuron when stimulated by norepinephrine in a feedback, autoregulatory fashion (see Chapter 5). However, stimulation of α_2 receptors (not shown in Fig. 6.9) results in activation of an inhibitory G protein, designated G_i , whose α subunit serves to inhibit the enzyme adenylyl cyclase, lowering the rate of synthesis for intracellular cAMP.

α_1 -Receptor Activation

Stimulation of an α_1 receptor by an agonist, such as phenylephrine or epinephrine (which has affinity for both α and β receptors), results in vasoconstriction of peripheral blood vessels, including vessels in the airway. The mechanism of action for this effect as mediated by the G protein-linked α_1 receptor is illustrated in Fig. 6.10. Stimulation of the α_1 receptor causes a conformational change in the receptor, which activates the G protein, designated G_q . With activation, GDP dissociates from the G protein; GTP binds to the α subunit of the G protein; and the α subunit dissociates from the

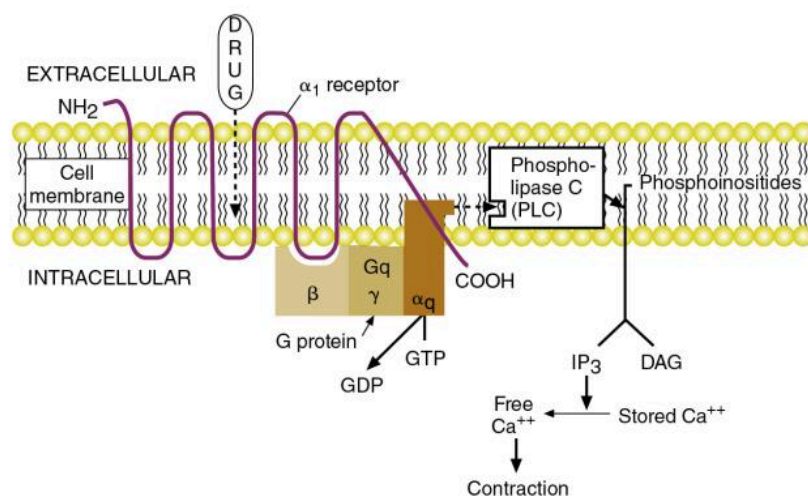
β - γ dimer, to activate the effector phospholipase C (PLC). Activation of the effector, PLC, leads to the conversion of membrane phosphoinositides into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 stimulates release of intracellular stores of calcium into the cytoplasm of the cell, and DAG activates protein kinase C. Contraction of vascular smooth muscle results.

Long-Acting β Agonists: Mechanism of Action

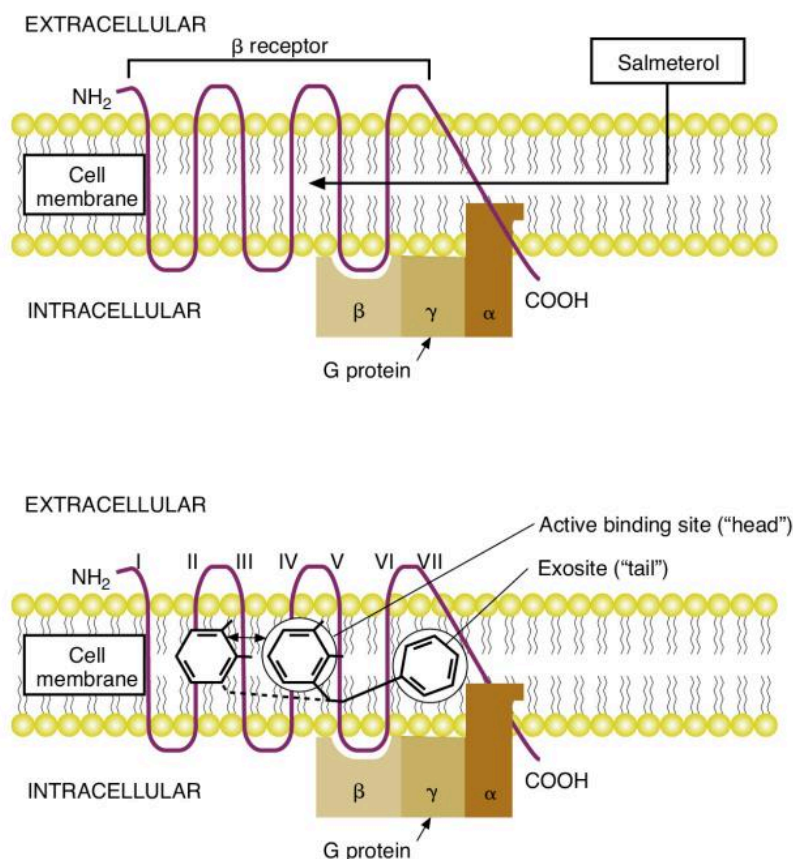
The mechanism of action for LABAs in providing sustained protection from bronchoconstriction differs to a degree from that of the previously described adrenergic bronchodilators. The difference in the pharmacodynamics of an LABA is reflected in its pharmacokinetics, with a slower onset and time to peak effect and a longer duration of action compared with previous adrenergic agents.

The structures of long-acting agents are shown in Fig. 6.7 for comparison. The agents are a modification of the saligenin albuterol, with a long nonpolar (i.e., *lipophilic*) N-substituted side chain. For example, salmeterol consists of a polar, or *hydrophilic*, phenyl ethanolamine “head” with a large lipophilic “tail” or side chain. As a result of this structure, salmeterol is lipophilic, in contrast to most SABAs, which are hydrophilic and approach the β receptor directly from the aqueous extracellular space. In contrast, salmeterol, as a lipophilic molecule, diffuses into the cell membrane phospholipid bilayer and approaches the β receptor laterally, as shown in Fig. 6.11. The lipophilic nonpolar side chain binds to an area of the β receptor referred to as the *exosite*, a hydrophobic region. With the side chain (“tail”) anchored in the exosite, the active saligenin “head” binds to and activates the β receptor at the same location as albuterol.

The binding properties of LABAs differ from those of albuterol and other SABAs. Because the side chain of long-acting agents is anchored at the exosite, the active “head” portion continually attaches to and detaches from the receptor site. This activity provides ongoing stimulation of the β receptor and is the basis for the persistent duration of action of long-acting agents. This model of activity is supported by studies of the effect of β antagonists on the β -agonist action of long-acting agents and molecular binding. If albuterol is attached to the β receptor, the smooth muscle relaxation can be fully reversed by a β -blocking agent, such as propranolol or sotalol, indicating a competitive blockade. When



• **Fig. 6.10** Diagram illustrating mechanism of action by which stimulation of the G protein-linked α_1 receptor by an α agonist causes smooth muscle contraction, which can result in vasoconstriction of blood vessels. Ca^{++} , calcium ion; COOH , carboxy; DAG, diacylglycerol; IP_3 , inositol 1,4,5-trisphosphate; GDP, guanosine diphosphate; GTP, guanosine triphosphate; NH_2 , amine group.



• **Fig. 6.11** Illustration of mechanism of action by which salmeterol, a long-acting β_2 -specific bronchodilator, interacts with the β receptor via an exosite anchor, that is, its lipophilic side chain (the “tail”), allowing continual stimulation of the receptor via its active binding site (the “head”). COOH , Carboxy; NH_2 , amine group.

the β -blocking agent is removed, there is no further relaxation of smooth muscle. The albuterol has been displaced, and the action of the drug is terminated. If an LABA stimulates a receptor, a β antagonist, such as propranolol, would also reverse the effect of relaxation. However, when the propranolol is removed from the tissue, the relaxant effect of the LABA is reestablished. This indicates that LABAs remain anchored in the receptor and are available to stimulate the β receptor continually after the blocking agent is removed.^{15,19–24}

Routes of Administration

β -Adrenergic bronchodilators are currently available for inhalation (MDI, nebulizer solution, DPI, Respimat), oral administration (tablets or syrup), and parenteral administration (injection), although not all agents are found in each form. Regardless of the route of administration, there are three general patterns to the time course of bronchodilation with drugs in this group. The *catecholamines* show a rapid onset of 1 to 3 minutes, a peak effect at about 15 to 20 minutes, and a rapid decline in effect after 1 hour. The *noncatecholamines* (resorcinols and saligenins), with the exception of salmeterol, show an onset of 5 to 15 minutes, a peak effect at 30 to 60 minutes, and a duration of effect of 4 to 6 hours. Salmeterol differs significantly, with a slower onset (>20 minutes) and peak effect (at about 3 hours) and a 12-hour

duration of effect. Formoterol and arformoterol are similar to salmeterol in duration but have an onset as rapid as that of albuterol. Olodaterol and vilanterol all have a duration of effect of at least 24 hours. Besides these general patterns, which depend on the type of drug used, the route of administration further affects the time course of a drug. Inhaled and injected adrenergic bronchodilators have a quicker onset compared with orally administered agents.

CLINICAL CONNECTION

Routes of administration for β agonists include inhalation (aerosol), oral, and parenteral; minimal side effects are seen with inhalation.

Inhalation Route

All the β -adrenergic bronchodilators marketed in the United States are available for inhalation delivery via an MDI, a nebulizer (including intermittent positive-pressure breathing nebulization), a DPI, or Respimat. Catecholamines must be given by inhalation because they are ineffective orally. Inhalation is the preferred route for administering β -adrenergic drugs for the following reasons:

- Onset is rapid.
- Smaller doses are needed compared with doses for oral use.

- Side effects, such as tremor and tachycardia, are reduced.
- Drug is delivered directly to the target organ (i.e., lung).
- Inhalation is painless and safe.

The use of aerosol delivery *during* an acute attack of airway obstruction has been questioned. However, several studies have failed to show substantial differences between inhaled and parenteral β -adrenergic agents in acute severe asthma.^{36,37} There is no reason to avoid these bronchodilators as inhaled aerosols during acute episodes.³⁸ The inhalation route targets the lung directly. Combining oral delivery with additional inhalation has been shown to produce good additive effects with albuterol.³⁹

The major difficulties with aerosol administration are the time needed for nebulization (5–10 minutes), the possible embarrassment of using an MDI in public or at school, and inability to use an MDI correctly. Difficulty in correctly using MDIs can be remedied by using spacer devices or, alternatively, by using gas-powered handheld nebulizers. DPIs can eliminate problems associated with nebulizers and MDIs.

Continuous Nebulization

Administration of inhaled adrenergic agents by continuous nebulization has been used to manage severe asthma, to avoid respiratory failure, intubation, and mechanical ventilation. The *Guidelines for the Diagnosis and Management of Asthma* released by NAEPP EPR 3 recommend 2.5 to 5 mg of albuterol by nebulizer every 20 minutes in three doses and 10 to 15 mg/hr by continuous nebulization. Because a nebulizer treatment takes approximately 10 minutes, giving three treatments every 20 minutes requires repeated therapist attendance. Continuous administration by nebulizer may simplify such frequent treatments. The use of continuous nebulization of β -agonist bronchodilators was reviewed by Fink and Dhand,⁴⁰ who presented a summary of studies, including dosages used. With continuous nebulization, there are no general standards for dosages other than the recommendation from NAEPP EPR 3; in the studies cited by Fink and Dhand,⁴⁰ dosages vary from 2.5 to 15 mg/hr and include schedules based on milligrams per kilogram per hour.

The effect and optimal use of continuous nebulization versus intermittent nebulization are unclear. In the five randomized controlled trials cited by Fink and Dhand,⁴⁰ there was similar improvement between continuous versus intermittent nebulization. One study by Lin et al.⁴¹ showed faster improvement with use of continuous nebulization in patients with FEV₁ less than 50% of predicted. A study by Camargo et al.⁴² compared high (7.5 mg) and low (2.5 mg) dosage of albuterol with both continuous and intermittent nebulization. FEV₁ improved more with continuous than intermittent nebulization, and the low dose of 2.5 mg was as effective as the higher dose of 7.5 mg with continuous administration. These and other results suggest that there is a benefit to continuous nebulization in severe airflow obstruction, but a dosage less than 10 to 15 mg/hr may be effective, with less toxicity. Less clinician time is required for the administration of continuous nebulization. Fink and Dhand⁴⁰ suggested that for emergency department patients who have severe airway obstruction and do not respond sufficiently after 1 hour of intermittent nebulization of β agonists, continuous nebulization offers a practical approach to optimal dosing in a cost-effective manner.

Delivery Methods. Several delivery methods to accomplish continuous nebulization have been tried and reported, including the following:

- Measured refilling of a small volume nebulizer (SVN)
- Volumetric infusion pump with SVN⁴³
- Large-reservoir nebulizer, such as the HEART or HOPE nebulizer

Toxicity and Monitoring. Continuous nebulization of β_2 agonists is not standard therapy, and patients receiving this treatment have serious airflow obstruction. Potential complications include cardiac arrhythmias, hypokalemia, and hyperglycemia. Unifocal premature ventricular contractions were reported in one patient by Portnoy et al.⁴⁴ Significant tremor may also occur. Subsensitization to continuous therapy was not observed by Portnoy et al. Close monitoring of patients receiving continuous β agonists is necessary and includes observation and cardiac and electrolyte monitoring. Selective β_2 agonists, such as albuterol, should be used to reduce side effects.

Oral Route

The oral route has the advantages of ease, simplicity, short time required for administration, and exact reproducibility and control of dosage. However, in terms of clinical effects, this is not the preferred route. The time course of oral β agonists differs from that of inhaled β agonists. The onset of action begins in about 1.5 hours, with a peak effect reached after 1 to 2 hours, and a duration of action between 3 and 6 hours.⁴⁵ Larger doses are required than with inhalation, and the frequency and degree of unwanted side effects increases substantially. Catecholamines are ineffective by mouth, as previously discussed. Noncatecholamine bronchodilators in the adrenergic group seem to lose their β_2 specificity with oral use, possibly because of the reduction of the side chain bulk in a first pass through the liver.⁴⁶ Patient compliance on a three- or four-times-daily schedule may be better than with a nebulizer. If this is the case with an individual patient and the side effects are tolerable, oral use may be indicated for bronchodilator therapy. The introduction of an oral tablet of albuterol with extended action properties (Vospire ER) offers the possibility of protection from bronchoconstriction for up to 12 hours. However, inhaled salmeterol, formoterol, and arformoterol offer 12-hour duration. Now agents, such as olodaterol, can provide 24-hour duration in one dose. Either the extended-release tablet or an LABA is advantageous in preventing nocturnal asthma and deterioration of flow rates in the morning.

Parenteral Route

β -Adrenergic bronchodilators have been given subcutaneously and intravenously, usually in the emergency management of acute asthma. Subcutaneously, epinephrine 0.3 mg (0.3 mL of 1:1000 strength), every 15 to 20 minutes up to 1 mg in 2 hours, and terbutaline, 0.25 mg (0.25 mL of a 1-mg/mL solution) repeated every 15 to 30 minutes, not exceeding 0.5 mg in 4 hours, have been used. Shim⁴⁷ suggested that for practical purposes, both aerosolized and subcutaneous routes should be used to manage acute obstruction, although there may be little difference in effect with use of these two routes. No difference in effect between epinephrine and terbutaline has been found when given subcutaneously.

The IV route has been used most commonly with isoproterenol and with albuterol. IV administration of these agents was thought to be useful during severe obstruction because these agents would be distributed throughout the lungs, whereas aerosol delivery

would not allow them to penetrate the periphery. This assumption is questionable for both subcutaneous and IV bronchodilator therapy because aerosols do exert an effect with obstruction. IV isoproterenol is not clearly advantageous as a bronchodilator, although this route is used for cardiac stimulation in shock and bradycardia. The dose-limiting factor is tachycardia. IV therapy is a last resort and requires an infusion pump, cardiac monitor, and close attention. Pediatric dosages range from 0.1 to 0.8 mcg/kg/min, and adult dosages range from 0.03 to 0.2 mcg/kg/min, until bronchial relaxation or side effects occur.⁴⁷ The combination of myocardial stimulation and hypoxia can cause serious arrhythmias; IV isoproterenol should be avoided in acute asthma, in favor of β_2 -specific agents. Albuterol has been given intravenously as a bolus of 100 to 500 mcg or by infusion of 4 to 25 mcg/min.⁴⁸ Although albuterol is more β_2 specific via aerosol compared with isoproterenol, the usefulness of IV administration compared with oral, aerosol, or subcutaneous administration is not clearly established.

Adverse Side Effects

Just as adrenergic bronchodilators exert a therapeutic effect by stimulation of α -adrenergic, β_1 -adrenergic, or β_2 -adrenergic receptors, they can likewise cause unwanted effects as a result of stimulation of these receptors. Generally, the term *side effect* indicates any effect other than the intended therapeutic effect. The most common clinically observed side effects of adrenergic bronchodilators are listed in [Box 6.2](#) and are briefly discussed. The number and severity of these side effects vary among patients; not every side effect is seen in every patient. The newer adrenergic agents (albuterol, levalbuterol, salmeterol, formoterol, arformoterol, olodaterol, and vilanterol) are much more β_2 specific compared with older agents, such as ephedrine, epinephrine, or isoproterenol, and because of this, there is a greater likelihood of cardiac stimulation causing tachycardia and blood pressure increases with the last three agents than with the newer drugs. The more recent agents are safe, and the side effects listed are more of a nuisance than a danger and are easily monitored and controlled by clinicians. The introduction of single-isomer β agonists, such as levalbuterol, may show further specificity and decrease in side effects, which are potentially caused by the detrimental effects of the (S)-isomer of β agonists.

• BOX 6.2 Side Effects Seen With β Agonist Use

- Tremor
- Palpitations and tachycardia
- Headache
- Insomnia
- Increase in blood pressure
- Nervousness
- Dizziness
- Nausea
- Tolerance to bronchodilator effect
- Loss of bronchoprotection
- Worsening ventilation-perfusion ratio (resulting in decreased partial pressure of arterial oxygen [PaO_2])
- Hypokalemia
- Bronchoconstrictor reaction to solution additives (small volume nebulizer [SVN]) and propellants (metered dose inhaler [MDI])

CLINICAL CONNECTION

Adverse side effects can occur with β agonists and include tremor (very common), headache, insomnia, bronchospasm (with metered dose inhaler [MDI] use), palpitations, and some tolerance.

Tremor

The annoying effect of muscle tremor with β agonists is caused by stimulation of β_2 receptors in skeletal muscle. It is dose related and is the dose-limiting side effect of the β_2 -specific agents, especially with oral administration. The adrenergic receptors mediating muscle tremor have been shown to be of the β_2 type.^{49,50} As shown previously, this side effect is much more noticeable with oral delivery, which provides a rationale for aerosol administration of these agents. Tolerance to the side effect of tremor usually develops after days to weeks with the oral route, and patients should be reassured of this when beginning to use these drugs.

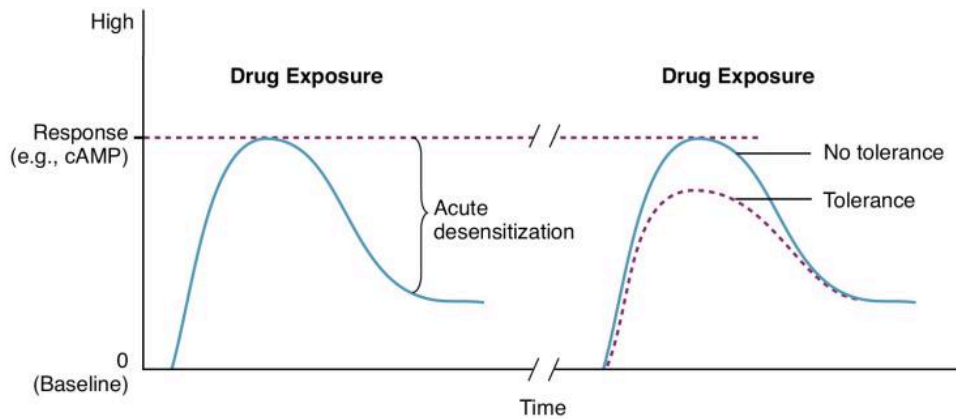
Cardiac Effects

The older adrenergic agents with strong β_1 -stimulating and α -stimulating effects were considered dangerous in the presence of congestive heart failure. The dose-limiting side effect of these agents is tachycardia. They increase cardiac output and oxygen consumption by stimulating β_1 receptors, leading to a decrease in cardiac efficiency, which is the work relative to oxygen consumption. Newer agents have a preferential β_2 effect to minimize cardiac stimulation. However, tachycardia may also occur with use of the newer agents, and there is evidence that this results from the presence of β_2 receptors, even in the heart.⁵¹ β_2 agonists cause vasodilation, and this can cause a reflex tachycardia. Despite this effect, some agents, such as terbutaline or albuterol, can actually improve cardiac performance. Albuterol and terbutaline can cause peripheral vasodilation and increase myocardial contractility without increasing oxygen demand by the heart.³⁴ The net effect is to reduce afterload and improve cardiac output with no oxygen cost. These agents are therefore attractive for use in cases of airway obstruction combined with congestive heart failure.

Seider et al.⁵² reported that neither heart rate nor frequency of premature beats was significantly affected by inhaled terbutaline or ipratropium bromide (an anticholinergic bronchodilator) in 14 patients with COPD and ischemic heart disease. Although there are no written standards, most health care practitioners do not accept a greater than 20% change in pretreatment pulse after bronchodilator therapy has been initiated. This is why it is important to check the pulse rate before, during, and after bronchodilator therapy to evaluate cardiac response. If the pulse rate has increased by greater than 20% relative to the pretreatment pulse, stopping treatment and providing referral to the prescribing health care practitioner may be warranted to prevent unwanted cardiac effects.

CLINICAL CONNECTION

Downregulation is the reduction of β receptors on the airway resulting from tolerance after long-term use of bronchodilators. Reversal of downregulation, which is known as *upregulation*, can be achieved with use of a corticosteroid.



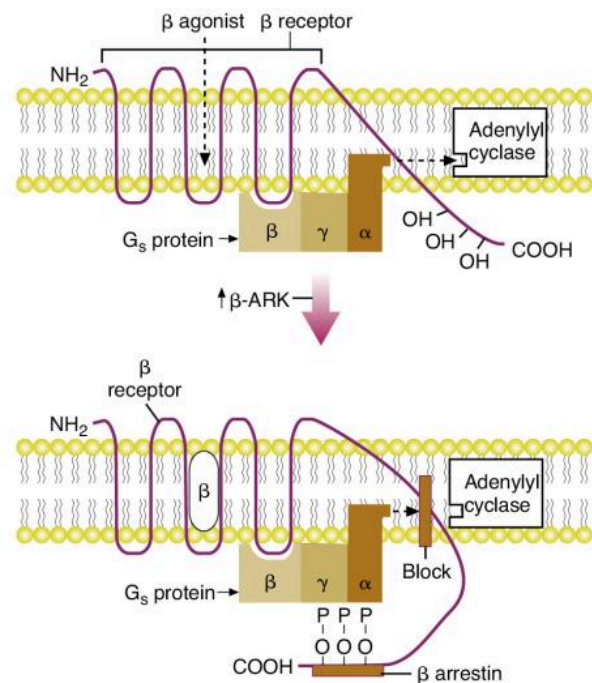
• **Fig. 6.12** Graphic representation of acute and long-term desensitization of the β -receptor response to β agonists. Cell response during actual receptor stimulation by agonist immediately declines (*left side*); subsequent exposure to drug would produce a lower peak initial response if tolerance or long-term desensitization occurs (*right side*). cAMP, Cyclic adenosine 3',5'-monophosphate.

Tolerance to Bronchodilator Effect

Adaptation to a drug with repeated use is a concern because such use of the drug is reducing its effectiveness. With β agonists, there is *in vitro* evidence of an acute desensitization of the β receptor within minutes of exposure to a β agonist, as well as a longer-term desensitization. Fig. 6.12 shows both an acute decrease in response during sustained exposure of the receptor to the agonist and a long-term decrease in maximal response with subsequent drug exposure. This decrease in bronchodilator response has been observed with SABAs and LABAs.

Exposure of cells with β receptors to isoproterenol causes a short-term, acute reduction in adenylyl cyclase activity and production of cAMP. The immediate desensitization is caused by an “uncoupling” of the receptor and the effector enzyme adenylyl cyclase.⁵³ A model for desensitization of the β receptor is diagrammed in Fig. 6.13. When stimulated by a β agonist, the β receptor goes into a low-affinity binding state (i.e., has reduced affinity for binding with a β agonist). Simultaneously, the β agonist causes an increase in cAMP, which increases protein kinase A, also referred to as β -adrenergic receptor kinase (β -ARK). β -ARK causes phosphorylation (transfer of phosphate groups [P]) of the hydroxyl groups (OH) on the carboxy-terminal portion of the β receptor. This phosphorylation induces binding of a protein named β -arrestin, which prevents the receptor from interacting with G_s and disrupts the coupling of G_s with the effector enzyme adenylyl cyclase. Removal of the β agonist causes dissociation of β -arrestin and the phosphate groups from the receptor, and the receptor returns to a fully active state.

Long-term desensitization is caused by a reduction in the number of β receptors; this is termed **downregulation**. Both norepinephrine and albuterol have caused a reduction of almost 50% *in vitro* in the number of β -adrenergic receptors in airway smooth muscle of guinea pigs.⁵³ Exposure of isolated human bronchus to isoproterenol or terbutaline produces similar desensitization.⁵⁴ Long-term desensitization, also illustrated in Fig. 6.12, is indicated by the lower peak response to subsequent administration of an adrenergic agonist.



• **Fig. 6.13** Model for β -receptor desensitization through phosphorylation of the β receptor at the carboxy-terminal site by β -adrenergic receptor kinase (β -ARK), blocking the action of the α_2 subunit on the effector enzyme adenylyl cyclase. COOH, Carboxy; NH_2 , amine group; O, oxygen; OH, hydroxyl groups; P, phosphate groups.

Although use of an inhaled β agonist does cause a reduction in peak effect, the bronchodilator response is still significant and stabilizes within several weeks with continued use.¹⁸ Such tolerance is not generally considered clinically important and does not contraindicate the use of these agents. The same phenomenon of tolerance is also responsible for diminished side effects, such as muscle tremor, among patients regularly using inhaled β -agonist bronchodilators.

In addition to loss of receptors (downregulation) by exposure to a β agonist, altered β -receptor function may be caused secondary

to inflammation. Increased levels of phospholipase A₂ (PLA₂) may destabilize membrane support of the β receptor, changing its function. Cytokines, such as interleukin-1 β (IL-1 β), may cause desensitization, and platelet-activating factor (PAF) inhibits the relaxing effect of isoproterenol on human tracheal tissue.

Corticosteroids can reverse the desensitization of β receptors and are said to have the ability to potentiate the response to β agonists.⁵⁵ Corticosteroids have the following effects in relation to β -agonist and β -receptor functions:

- Corticosteroids increase the proportion of β receptors expressed on the cell membrane (*upregulation*).
- Corticosteroids increase the proportion of β receptors in the high-affinity binding state.
- Corticosteroids inhibit the release and action of inflammatory mediators, such as PLA₂, cytokines, and PAF.

β agonists may have a positive effect on corticosteroid function and activity. A review by Sin and Man²⁷ explored possible mechanisms for the beneficial interaction of β agonists and corticosteroids.

Loss of Bronchoprotection

Ahrens et al.⁵⁶ found a distinction between the *bronchodilating effect* and the *bronchoprotective effect* of β agonists. The bronchodilating effect of a β agonist can be measured on the basis of air-flow change, as indicated by a change in FEV₁ or peak expiratory flow rate (PEFR). The bronchoprotective effect refers to the reaction of the airways to challenge by provocative stimuli, such as allergens or irritants, and is measured with doses of histamine, methacholine, or cold air. Ahrens et al.⁵⁴ found that the protective effect of agonists, such as albuterol, declines more rapidly than their bronchodilating effect. Not only is there a difference in time between these effects, but it was also found that tolerance occurs with the bronchoprotective effect of a β agonist, just as with the bronchodilating effect. O'Connor et al.⁵⁷ demonstrated the difference in a dose of adenosine monophosphate (AMP) and methacholine required to induce a 20% decline in FEV₁ (PC₂₀) after the inhalation of terbutaline compared with a placebo before and after 7 days of steady treatment with terbutaline. Airway response to challenge is occurred with a significantly lower dose of either AMP or methacholine in subjects with mild asthma after 7 days of β -agonist exposure, showing tolerance to the protective effect of bronchodilator. The development of tolerance to the bronchoprotective effect of the long-acting β agonist salmeterol was shown to occur both in the absence of corticosteroid therapy (Bhagat et al.⁵⁸) and with concomitant inhaled corticosteroid treatment (Kalra et al.⁵⁹). In a study by Rosenthal et al.,⁶⁰ after the first 4 weeks of regular treatment with salmeterol, there was no increase in bronchial hyperresponsiveness or loss of bronchoprotection. Sustained improvements were seen in pulmonary function and asthma symptom control.⁶⁰

The mechanism underlying the increase in bronchial hyperresponsiveness with use of β agonists is unclear. Evidence accumulating on the effects of the (S)-isomer of β agonists suggests a possible cause.⁶¹ The same effects could conceivably be implicated in the reduction in maximal bronchodilator effect with repeated use.

Central Nervous System Effects

Commonly reported side effects of the adrenergic bronchodilators include headache, nervousness, irritability, anxiety, and

insomnia, which are caused by CNS stimulation. Feelings of nervousness or anxiety may be caused by the muscle tremor seen with use of these drugs, rather than by direct CNS stimulation. Excessive stimulation of the CNS, or at least symptoms of such, should be noted by clinicians and may warrant evaluation of the dosage used.

Fall in Arterial Oxygen Pressure

A decrease in partial pressure of arterial oxygen (PaO₂) has been noted with isoproterenol administration during asthmatic bronchospasm when ventilation improves and the exacerbation is relieved. The same effect has subsequently been noted with newer β agonists, such as albuterol and salmeterol.⁶² The mechanism seems to be an increase in perfusion (i.e., blood flow) of poorly ventilated portions of the lung. It is known that regional alveolar hypoxia produces regional pulmonary vasoconstriction in an effort to shunt perfusion to the areas of the lung with higher oxygen tension. This vasoconstriction is probably accomplished by α -sympathetic receptors.⁶³

Administration of inhaled β agonists may reverse hypoxic pulmonary vasoconstriction by β_2 stimulation, which increases perfusion to under-ventilated lung regions.⁶⁴ Preferential delivery of the inhaled aerosol to better-ventilated lung regions increases the ventilation-perfusion mismatch. It has been noted that such decreases in PaO₂ are statistically significant but physiologically may be negligible.^{62,65} Oxygen tension decreases most in subjects with the highest initial PaO₂. Decreases in PaO₂ rarely exceed 10 mm Hg, and the PaO₂ values tend to be on the flat portion of the oxyhemoglobin curve so that decreases in saturation of arterial oxygen (SaO₂) are minimized. Oxygen tensions usually return to baseline within 30 minutes.

CLINICAL CONNECTION

High doses of β agonists can increase glucose and decrease serum potassium levels. It is possible the use of high doses of an inhaled β agonist can treat hyperkalemia.

Metabolic Disturbances

Adrenergic bronchodilators can increase blood glucose and insulin levels and decrease serum potassium levels. This is a normal effect of sympathomimetics. In patients with diabetes, clinicians should be aware of a possible effect on glucose and insulin levels. Hypokalemia has also been reported after parenteral administration of albuterol and epinephrine.⁶⁶ The clinical importance of this side effect is controversial, and it would be of concern mainly for patients with cardiac disease or in interpreting serum potassium levels obtained shortly after use of adrenergic bronchodilators. The mechanism of the effect on potassium is probably activation of the sodium-potassium pump by the β receptor, with enhanced transport of potassium from the extracellular compartment to the intracellular compartment. Such metabolic effects are minimized with inhaled aerosols of β -adrenergic agents because plasma levels of the drug remain low. However, the use of large inhaled doses and of multiple doses, such as utilizing short-acting and long-acting sympathomimetics together, should warrant monitoring of potassium.

Propellant Toxicity and Paradoxical Bronchospasm

The use of MDIs powered by CFC (e.g., Freon) did cause bronchospasm of hyperreactive airways. This reaction to the propellant was shown by Huchon et al.,⁶⁷ who found that 7% of 175 subjects who used an MDI with a placebo and propellant experienced a decrease of 10% or more in FEV₁. The incidence was about 4% when using an MDI with metaproterenol and propellant, probably because the bronchodilating effect overcame the propellant effect. In most cases, bronchospasms last less than 3 minutes. There is apparently no noticeable difference in adverse reactions among patients using a CFC MDI and patients using an HFA MDI.⁶⁷ A dry powder formulation is an ideal alternative formulation to an MDI if sensitivity to propellants exists, assuming drug availability and adequate inspiratory flow rate. Use of a nebulizer instead of an MDI may also be considered if bronchospasm occurs in a patient. Finally, the oral route offers an alternative to the inhalation route of administration. Asmus et al.⁶⁸ reviewed the literature on paradoxical bronchospasm occurring with use of inhalation aerosols.

Sensitivity to Additives

An increasingly publicized problem for individuals with hyperreactive airways is sensitivity to sulfite preservatives, with resulting bronchospasm. Sulfites are used as preservatives in food products and are used as antioxidants in bronchodilator solutions to prevent degradation and inactivation. Sulfites include sodium or potassium sulfite, bisulfite, and metabisulfite. When a sulfite is placed in solution, at a warm temperature in an acid pH, such as saliva, it converts to sulfurous acid and sulfur dioxide. Sulfur dioxide is known to cause bronchoconstriction in patients with asthma. A solution of racemic epinephrine is known to contain sulfites as preservatives. There have been reports of coughing, wheezing, and pruritus after use of sulfite-containing bronchodilators.

Other additives and preservatives that can potentially have an effect on airway smooth muscle include benzalkonium chloride (BAC), ethylenediamine tetraacetic acid (EDTA), and hydrochloric or sulfuric acid to adjust pH of the solution. Asmus et al.⁶⁸ recommended that only additive-free, sterile-filled unit-dose bronchodilator solutions be used for nebulizer treatment of acute airflow obstruction, especially if doses are given hourly or continuously. Clinicians should check aerosol formulations for BAC or EDTA and consider these as possible causes if symptoms of bronchoconstriction occur.

Compatibility of Other Agents With Bronchodilators

Respiratory therapists often mix multiple agents into the liquid medication cup of nebulizer. However, mixing most, if not all, agents with other agents is not FDA approved.

Several studies have tested the compatibility of common bronchodilators with other agents used in respiratory care. Kamin et al.⁶⁹ found no chemical changes when they mixed albuterol with ipratropium, cromolyn, budesonide, tobramycin, or colistin. For a more complete listing, see [Appendix C](#). Bonasia et al.⁷⁰ reported that levalbuterol is compatible with ipratropium,

cromolyn, acetylcysteine, and budesonide for at least 30 minutes at room temperature. Akapo et al.⁷¹ discovered that formoterol nebulizer solution was compatible with ipratropium, cromolyn, acetylcysteine, and budesonide.

Mixing solutions is common practice, and the literature supports the mixing of many common agents used in respiratory care. Mixing of agents should be done with caution, however. Special attention should be directed to the nebulizer in use and its function.

β-Agonist Controversy

The **asthma paradox** is a descriptive phrase for the increasing incidence of asthma morbidity, especially asthma mortality, despite the advances in the understanding of asthma and the availability of improved drugs to treat asthma. Many studies have implicated the use of SABAs in asthma near-death emergencies and deaths,^{72,73} worsening clinical outcomes,^{74,75} and increased hyperreactivity.^{76,77} The events described in these studies may have been related to lack of corticosteroid use, leaving uncontrolled asthma symptoms to be treated only with SABAs.

Short-acting drugs, such as albuterol, and long-acting agents, such as salmeterol, have not, in general, been associated with a significant worsening of asthma.⁷⁸ However, more recent evidence has indicated that LABAs may have a potential to increase asthma hospitalization or cause death.^{34,35} It has been noted that regular use of fenoterol and isoproterenol, but not other β agonists, may lead to poor asthma control.⁶¹ Tolerance to the bronchodilator effect does occur with the use of β agonists, although this tolerance stabilizes and does not progress. There is an increase in bronchial hyperreactivity after institution of regular β-agonist therapy, which is not well explained. Evidence suggests that this effect may be caused or enhanced by the (S)-enantiomer of β agonists and has a range of proinflammatory effects.

Asthma Morbidity and Mortality

KEY POINT

The β agonists have been questioned as a possible factor in the increase in asthma mortality, leading to the “β-agonist controversy.”

A complete analysis of the relationship between β agonists and worsening asthma based on the literature seems to indicate that a class effect of these drugs causing deterioration of asthma does *not* exist.⁶¹ Although it is unclear that β-agonist use increases the risk of morbidity or death, asthma mortality is reported to be increasing in the United States and worldwide despite more available treatment options, including β₂-specific and longer-acting adrenergic bronchodilators.⁷⁹ There are several causes—not all involving β-agonist therapy—that may potentially lead to worsening asthma severity:

- Use of β agonists may allow allergic individuals to expose themselves to allergens and stimuli, with no immediate symptoms to warn them, but progressive airway inflammation and increasing bronchial hyperresponsiveness occur.
- Repeated self-administration of β agonists gives temporary relief of asthma symptoms through bronchodilation, which may cause underestimation of severity and delay in seeking medical help. β agonists do not block progressive airway

inflammation, which can lead to death from lethal airway obstruction and hypoxia.

- Use of β agonists to alleviate symptoms of wheezing and resistance may lead to insufficient use—through poor patient education, poor patient compliance, or both—of antiinflammatory therapy to control the basic inflammatory nature of asthma.
- Accumulation of the (S)-isomer with racemic β agonists could exert a detrimental effect on asthma control.
- There is increased airway irritation with environmental pollution and lifestyle changes.⁸⁰

In evaluating β -agonist therapy in asthma, one must evaluate concomitant antiinflammatory therapy (or the lack of it) and environmental management of asthma.

RESPIRATORY CARE ASSESSMENT OF β -AGONIST THERAPY

Before Treatment

- Assess the effectiveness of drug therapy on the basis of indication for the aerosol agent: Presence of reversible airflow resulting from primary bronchospasm or obstruction secondary to an inflammatory response or secretions, either acute or chronic.
- Monitor flow rates by using bedside peak flow meters, portable spirometry, or laboratory evaluation of pulmonary function before and after bronchodilator studies to assess reversibility of airflow obstruction.
- Perform respiratory assessment of breathing rate and pattern and breath sounds by auscultation, before and after treatment.
- Assess pulse before, during, and after treatment; a 20% increase from baseline may constitute changing medication or discontinuing therapy.

During Treatment and Short Term

- Assess the patient's subjective reaction to treatment for any change in breathing effort or pattern.
- Assess arterial blood gases or pulse oximeter saturation, as needed, for acute states with asthma or COPD, to monitor changes in ventilation and gas exchange (oxygenation).
- Note the effect of β agonists on blood glucose (increase) and potassium (decrease) laboratory values, if high doses, such as with continuous nebulization or emergency department treatment, are used.

Long Term

- Monitor pulmonary function studies of lung volume, capacity, and airflow.
- Instruct patients with asthma in the use and interpretation of disposable peak flow meters to assess the severity of asthma episodes and to ensure that there is an action plan for treatment modification.
- Patient education should emphasize that β agonists do not treat underlying inflammation or prevent progression of asthma, and additional antiinflammatory treatment or more aggressive

medical therapy may be needed if there is a poor response to the rescue β agonist.

- Instruct on, and then verify, the correct use of the aerosol delivery device (SVN, MDI, reservoir, DPI).
- Instruct patients in the use, assembly, and especially cleaning of aerosol inhalation devices.

For Long-Acting β Agonists

- Assess ongoing lung function, including predose forced expiratory volume in 1 second (FEV1) over time and variability in peak expiratory flows.
- Assess amount of rescue β -agonist use and nocturnal symptoms.
- Assess number of exacerbations, unscheduled clinic visits, and hospitalizations.
- Assess days of absence resulting from symptoms.
- Assess ability to reduce the dose of concomitant inhaled corticosteroids.

General Contraindications

- Bronchodilators are generally safe. However, regular, long-term use of short-acting and long-acting bronchodilators is not recommended.
- Use of bronchodilator therapy in patients with cardiac problems should be closely monitored.
- Patients with chronic disease (cystic fibrosis, COPD, and asthma) may be less responsive to bronchodilator therapy, possibly because of side effects from long-term use.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify an adrenergic bronchodilator used clinically that is a catecholamine.
2. Which catecholamine has been used as a bronchodilator and is commonly given to treat allergic reaction by self-injection?
3. What is the duration of action of the catecholamine bronchodilators?
4. Identify two advantages introduced with the modifications of the catecholamine structure in adrenergic bronchodilators.
5. Identify the usual dose by aerosol for a small volume nebulizer (SVN) for levalbuterol and albuterol.
6. What is an extremely common side effect with β_2 -adrenergic bronchodilators?
7. Identify the approximate duration of action for racemic epinephrine, albuterol, salmeterol, and olodaterol.
8. Identify the generic drug for each of the following brand names: Brovana, Serevent Diskus, and Ventolin HFA.
9. Which route of administration is more likely to have greater severity of side effects with a β -agonist oral or inhaled aerosol?
10. You notice a pinkish tinge to aerosol rainout in the large-bore tubing connecting a patient's mouthpiece to a nebulizer after a treatment with racemic epinephrine; what has caused this?
11. A patient exhibits paradoxical bronchoconstriction from the propellant when using an hydrofluoroalkane metered dose inhaler (HFA MDI). Suggest an alternative for the patient.
12. Would you suggest use of salmeterol to a patient with asthma who experiences occasional symptoms of wheezing and chest tightness, which respond well to an inhaled β agonist?
13. Suggest a β agonist that would be appropriate for the patient in Question 12.

CLINICAL SCENARIO

A 24-year-old White man moved to the metropolitan Atlanta area in the fall of last year. He presents to your outpatient clinic with a complaint of difficulty breathing. He has no history of asthma or other previous pulmonary disease. He is an accountant with a medium-size firm. He noticed a few “chest colds” from October through January, but these resolved with over-the-counter (OTC) cold medications, such as decongestants and cough suppressants. It is now late May, and during a round of golf he experienced difficulty breathing. During the interview, he described a tightness in his chest and the sound of wheezing. The golf course had recently been mown. The pollen count was quite high at the time, and there was an increase in the ozone concentration, leading to a smog alert on the day of his round. He also complained of waking up several times during the night with mild shortness of breath.

His respiratory rate (RR) is 14 breaths/min, with no obvious distress at rest; blood pressure (BP) is 128/74 mm Hg; heart rate (HR) is 76 beats/min; and temperature (T) is within normal limits. His oxygen saturation by pulse oximetry (SpO₂) is 93% on room air. You detect mild expiratory wheezing bilaterally on auscultation.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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7

Anticholinergic (Parasympatholytic) Bronchodilators

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Clinical Indications for Use

- Indication for Anticholinergic Bronchodilators
- Indication for Combined Anticholinergic and β -Agonist Bronchodilators
- Anticholinergic Nasal Spray

Specific Anticholinergic (Parasympatholytic) Agents

Clinical Pharmacology

- Structure–Activity Relationships
- Pharmacologic Effects of Anticholinergic (Muscarinic Antagonist) Agents
 - Tertiary Ammonium Compounds*
 - Quaternary Ammonium Compounds*

Mechanism of Action

- Vagally Mediated Reflex Bronchoconstriction
- Muscarinic Receptor Subtypes

Adverse Effects

Clinical Application

- Use in Chronic Obstructive Pulmonary Disease
- Use in Asthma
- Combination Therapy: β -Adrenergic and Anticholinergic Agents in Chronic Obstructive Pulmonary Disease
 - Additive Effect of β Agonists and Anticholinergic Agents*
 - Sequence of Administration*

Respiratory Care Assessment of Anticholinergic Bronchodilator Therapy

- Before Treatment
- During Treatment and Short Term
- Long Term
- General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to anticholinergic bronchodilators
2. Differentiate between *parasympathomimetic* and *parasympatholytic*
3. Differentiate between *cholinergic* and *anticholinergic*
4. Differentiate between *muscarinic* and *antimuscarinic*
5. List all available anticholinergic agents used in respiratory therapy
6. Discuss the indication for anticholinergic agents
7. Explain the mechanism of action for anticholinergic agents
8. Identify the route of administration available for anticholinergic agents
9. Discuss adverse effects for anticholinergic agents
10. Discuss the clinical application for anticholinergic agents

KEY TERMS AND DEFINITIONS

Anticholinergic bronchodilator Agent that blocks parasympathetic nervous fibers, allowing relaxation of smooth muscle in the airway.

Antimuscarinic bronchodilator Same as anticholinergic bronchodilator—agent that blocks the effect of acetylcholine (Ach) at the cholinergic site.

Cholinergic Agent that produces the effect of Ach.

Muscarinic Same as cholinergic—agent that produces the effect of Ach or an agent that mimics Ach.

Parasympatholytic Blocking parasympathetic nervous fibers.

Parasympathomimetic Producing effects similar to the parasympathetic nervous system.

This chapter discusses a second class of bronchodilators: anticholinergic agents. Anticholinergic drugs also known as muscarinic antagonists given by inhaled aerosol can block cholinergic-induced airway constriction. The chapter reviews their mechanism of action and their pharmacologic effects, based on their structural differences. Specific agents are profiled, and their clinical effect in chronic obstructive pulmonary disease (COPD) and asthma is discussed.

Clinical Indications for Use

KEY POINT

Anticholinergic agents given by inhalation are a second class of bronchodilating agents.

CLINICAL CONNECTION

Anticholinergic agents, also known as *muscarinic antagonists*, are often separated into short-acting muscarinic antagonists (SAMAs) and long-acting muscarinic antagonists (LAMAs).

Indication for Anticholinergic Bronchodilators

Ipratropium, acclidinium, glycopyrrolate, tiotropium, revefenacin, and umeclidinium are indicated as bronchodilators for maintenance treatment in COPD, including chronic bronchitis and emphysema. Ipratropium and tiotropium are used and may be indicated in some individuals with asthma. Tiotropium has recently been approved as an add-on treatment in the control of persistent asthma for patients as young as 6 years of age.

Indication for Combined Anticholinergic and β -Agonist Bronchodilators

A combination anticholinergic and β agonist, such as ipratropium and albuterol (Combivent Respimat), umeclidinium and vilanterol (Anoro Ellipta), acclidinium and formoterol (Duaklir Pressair), glycopyrrolate and formoterol (Bevespi Aerosphere), and tiotropium and olodaterol (Stiloto Respimat) are indicated for use in patients who receive maintenance treatment for COPD and require additional bronchodilation for relief of airflow obstruction. Ipratropium is also commonly used in addition to β agonists in severe asthma, especially bronchoconstriction that does not respond well to β -agonist therapy.

Anticholinergic Nasal Spray

A nasal spray formulation is indicated for symptomatic relief of allergic and nonallergic perennial rhinitis and the common cold.

Specific Anticholinergic (Parasympatholytic) Agents

Parasympatholytic (anticholinergic, or **antimuscarinic**) agents that are given by aerosol include single agents as well as agents in combination. Table 7.1 provides dosage and administration information for each agent.

Atropine sulfate had been administered as a nebulized solution by using either the injectable solution or, preferably, solutions

marketed for aerosolization; however, this agent is no longer aerosolized. Duration of bronchodilation and the incidence of side effects are dose dependent. Dosages for children based on dose-response curves had been given as 0.05 mg/kg three or four times daily.¹ Dosages for adults are based on a schedule of 0.025 mg/kg three or four times daily.² Although greater bronchodilation and duration were seen with dosage schedules of 0.05 or 0.1 mg/kg for adults, the side effects of dry mouth, blurred vision, and tachycardia became unacceptable. Because it is a tertiary ammonium compound and not fully ionized, atropine is readily absorbed from the gastrointestinal tract and respiratory mucosa. Systemic side effects (which are discussed subsequently) were seen in doses required for effective bronchodilation when given as an inhaled aerosol. The drug is not recommended for inhalation as a bronchodilator because of its widespread distribution in the body and the availability of the approved agents.

Ipratropium bromide (Atrovent) is a nonselective antagonist of the muscarinic receptors M_1 , M_2 , and M_3 (for a more detailed discussion, see Chapter 5). Ipratropium is currently available in two formulations for bronchodilator use: as a hydrofluoroalkane (HFA)-propelled metered dose inhaler (MDI) with 17 mcg/puff and as a nebulizer solution of 0.02% concentration in a 2.5-mL vial, giving a 500-mcg dose per treatment. One other option for the delivery of ipratropium in combination with albuterol is the soft-mist, propellant-free Respimat inhaler. As a quaternary ammonium derivative of atropine, ipratropium is fully ionized and does not distribute well across lipid membranes, limiting its distribution mostly to the lung when inhaled. Ipratropium is approved specifically for the maintenance treatment of airflow obstruction in COPD.

Ipratropium is poorly absorbed into the circulation from both the nasal mucosa, when given by nasal spray, and the airway, when inhaled orally by aerosol. Approximately 20% of the nasal dose and of the MDI dose is absorbed, with only 2% of the larger nebulizer solution absorbed into the bloodstream. Ipratropium is partially metabolized by ester hydrolysis into inactive products. It is minimally bound to plasma proteins, such as albumin (less than 9%), and the elimination half-life is about 1.6 hours.

The profile of clinical effect for ipratropium differs from that of inhaled β -adrenergic agonists. The onset of bronchodilation begins within minutes but proceeds more slowly to a peak effect 1 to 2 hours after inhalation. The effect of β agonists can peak between 20 and 30 minutes, depending on the agent. In asthma, the duration of bronchodilator effect is about the same for ipratropium as for β agonists. In COPD, the duration is longer by 1 to 2 hours.³

Ipratropium bromide (nasal spray) is also available for treatment of rhinopathies and rhinorrhea, including nonallergic perennial rhinitis, viral infectious rhinitis (colds), and allergic rhinitis, if intranasal corticosteroids fail to control symptoms.⁴ The nasal spray is available as a 0.003% and 0.06% solution delivering 21 and 42 mcg/spray, respectively, two sprays per nostril three or four times daily. Optimal dosage varies. Intranasal ipratropium has been shown to significantly reduce the volume of nasal secretions and symptoms in patients with allergic rhinitis and in patients with nonallergic rhinitis.⁴ Side effects with the nasal spray are largely local and have included nasal dryness, itching, and epistaxis in a few patients. Dry mouth and dry throat have also occurred. Systemic symptoms, such as blurred vision or urinary hesitancy, are rare.

Ipratropium and albuterol (Combivent Respimat) is a combination utilizing a soft-mist inhaler known as the Respimat (see Chapter 3), providing 20 mcg/puff of ipratropium and 100 mcg/

TABLE 7.1 Inhaled Anticholinergic Bronchodilator Agents*

Drug	Brand Name	Adult Dosage	Time Course (Onset, Peak, Duration)
Ipratropium bromide	Atrovent HFA	HFA MDI: 17 mcg/puff; 2 puffs qid SVN: 0.02% solution (0.2 mg/mL), 500 mcg tid, qid Nasal spray: 21 & 42 mcg; 2 sprays per nostril 2–4 times daily	Onset: 15–30 min Peak: 1–2 hr Duration: 6 hr
Ipratropium bromide and albuterol	Combivent Respimat	SMI: ipratropium 20 mcg/puff and albuterol 100 mcg/puff, 1 inhalation qid SVN: ipratropium 0.5 mg and albuterol 2.5 mg	Onset: 15 min Peak: 1–2 hr Duration: 6 hr
Acclidinium bromide	Tudorza Pressair	DPI: 400 mcg/inhalation, 1 inhalation bid	Onset: 10 min Peak: 2 hr Duration: 12
Acclidinium Bromide and formoterol	Duaklir Pressair	DPI: 400 mcg/12 mcg inhalation bid	Onset: 10–20 min Peak: 30 min–2 hr Duration: 12 hr
Glycopyrrolate bromide	Lonhala Magnair	VMN: 25 mcg/1 mL bid	Onset: 15–30 min Peak: 1–2 hr Duration: 12 hr
Glycopyrrolate bromide and formoterol	Bevespi Aerosphere	MDI: 9 mcg/inhalation and 4.8 mcg/inhalation formoterol bid	Onset: 5–15 min Peak: 30 min–1 hr Duration: 12 hr
Revefenacin	Yupelri	SVN: One ampule (175 mcg/3mL) once daily	Onset: 45 min Peak: 2–3 hr Duration: 24 hr
Tiotropium bromide	Spiriva; Spiriva Respimat	DPI: 18 µg/inhalation, 1 inhalation/1 capsule once daily SMI: 2.5 mcg/inhalation, 2 inhalations once daily (COPD) SMI: 1.25 mcg/inhalation, 2 inhalations once daily (asthma; 6 years and older)	Onset: 30 min Peak: 1–3 hr Duration: 24 hr
Tiotropium bromide and olodaterol	Stiolto Respimat	SMI: tiotropium 2.5 mcg/inhalation and olodaterol 2.5 mcg/inhalation, 2 inhalations once daily	Onset: 15 min Peak: 1–2 hr Duration: 24 hr
Umeclidinium bromide	Incruse Ellipta	DPI: 62.5 mcg/inhalation, 1 inhalation daily	Onset: 5–15 min Peak: 1–3 hr Duration: 24 hr
Umeclidinium bromide and vilanterol	Anoro Ellipta	DPI: umeclidinium 62.5 mcg/inhalation and vilanterol 25 mcg/inhalation, 1 inhalation daily	Onset: 5–15 min Peak: 1–3 hr Duration: 24 hr

*A holding chamber is recommended with MDI administration to prevent accidental eye exposure.

Bid, Twice daily; *COPD*, chronic obstructive pulmonary disease; *DPI*, dry powder inhaler; *HFA*, hydrofluoroalkane; *MDI*, metered dose inhaler; *qid*, four times daily; *SMI*, soft-mist inhaler (Respimat); *SVN*, small volume nebulizer; *tid*, three times daily; *VMN*, vibrating mesh nebulizer.

puff of albuterol. The combination therapy has been shown to be more effective in stable COPD than either agent alone.⁵ The chlorofluorocarbon (CFC) version of Combivent was removed from market on December 31, 2013. Additionally, this agent is available as a nebulized solution of ipratropium (0.5 mg) and an albuterol base (2.5 mg).

Glycopyrrolate (Lonhala) is a quaternary ammonium derivative of atropine that, like ipratropium, does not distribute well across lipid membranes in the body. It is usually administered parenterally as an antimuscarinic agent during reversal of neuromuscular blockade as an alternative to atropine; it has fewer ocular

or central nervous system (CNS) side effects. The injectable solution has been nebulized in a 1-mg dose for bronchodilation. Gal et al.⁶ reported a comparison of glycopyrrolate with atropine and established dose–response curves. Glycopyrrolate has an onset of action of approximately 15 to 30 minutes, a peak effect at 0.5 to 1 hour, and a duration of approximately 12 hours, attaching to the M1–M3 receptors. Tashkin and Gross⁷ provided a review of glycopyrrolate's effectiveness as monotherapy and in combination in the treatment of COPD. Currently, glycopyrrolate is approved by the US Food and Drug Administration (FDA) for treatment of COPD twice daily in a liquid form utilizing a vibrating mesh

nebulizer (Lohala Magnair). Additionally, glycopyrrolate is found in combination with formoterol (Bevespi Aerosphere) as an MDI to treat COPD.

Revefenacin (Yupelri) is a long-acting muscarinic antagonist that is available as an inhalation solution. The agent is like other anticholinergics and has affinity the inhibition of M₃ receptor leading to bronchodilation. Revefenacin is currently approved for treatment of COPD utilizing a standard nebulizer.

Tiotropium bromide (Spiriva), a muscarinic receptor antagonist, is a long-acting bronchodilator. It is a quaternary ammonium compound structurally related to ipratropium. Similar to ipratropium, tiotropium is poorly absorbed after inhalation. Inhalation of a single dose gives a peak plasma level within 5 minutes with a rapid decline to very low levels within 1 hour.^{8,9} Tiotropium exhibits receptor subtype selectivity for M₁ and M₃ receptors. The drug binds to all three muscarinic receptors (M₁, M₂, and M₃) but dissociates much more slowly than ipratropium from the M₁ and M₃ receptors. This results in a selectivity of action on the M₁ and M₃ receptors. Atropine and ipratropium block all three types of muscarinic receptors. The M₂ receptor is an autoreceptor inhibiting further release of acetylcholine (ACh) so that blockade can increase ACh release and may offset the bronchodilating effect of atropine or ipratropium.⁸ In patients with COPD, tiotropium gives a bronchodilating effect for up to 24 hours with an adequate dose. The effect of tiotropium can be seen for 32 hours; however, it dips between 16 and 24 hours because of the circadian rhythm. The drug also gives a prolonged, dose-dependent protection against inhaled methacholine challenge.¹⁰

CLINICAL CONNECTION

Anticholinergic bronchodilators are specifically *parasympatholytic*, that is, *antimuscarinic* agents, blocking the effect of acetylcholine (ACh) at the cholinergic (muscarinic) receptors on bronchial smooth muscle.

Several studies have examined the bronchodilating effect of various doses of tiotropium compared with placebo and ipratropium.¹⁰ Tiotropium reduces COPD exacerbations and hospitalizations, improves quality-of-life symptoms, and may slow the decline in a patient's forced expiratory volume in 1 second (FEV₁).¹¹

In the United States, tiotropium is available as a DPI and as a soft-mist, propellant-free Respimat inhaler. Spiriva Respimat, approved in September 2014, provides 2.5 mcg per actuation. The recommended dose is two actuations once daily. Additionally, Spiriva Respimat is approved for use in asthma as an add-on treatment. It has shown the ability to increase lung function without any adverse events to control asthma.¹² Rodrigo and Castro-Rodríguez found that add-on therapy with tiotropium assisted in reducing exacerbations of patients with asthma.¹³ The recommended dosing for the maintenance treatment of asthma is two inhalations of 1.25 mcg, once daily for patients age 6 years and older. Hamelmann and Szeffer found that add-on therapy of tiotropium in children and adolescents was safe and effective.¹⁴ Tiotropium bromide and olodaterol (Stiolto Respimat) is a combination agent providing 2.5 mcg of tiotropium and 2.5 mcg of olodaterol—a long-acting anticholinergic and β agonist used to treat airflow limitations in COPD—once daily. Stiolto Respimat, approved in May 2015, should not be used to treat asthma or acute deterioration of COPD. The recommended dosage is two actuations once daily.

Acclidinium bromide (Tudorza Pressair) is a long-acting, inhaled anticholinergic developed by Forest Laboratories (New York, New York) and approved by the FDA in July 2012 as a maintenance treatment for COPD.¹⁵ This agent is a potent antagonist of all muscarinic receptors, dissociating slowly at M₁ and in a shorter time at M₂, indicating the potential to provide sustained bronchodilation that is similar in action to tiotropium.¹⁶ Acclidinium is rapidly hydrolyzed in human plasma in contrast to ipratropium and tiotropium.^{16,17} This rapid hydrolysis results in very low and transient systemic exposure, suggesting a reduced potential for systemic side effects.^{16,17}

Early clinical studies in healthy subjects confirmed the low systemic bioavailability and favorable safety profile of single and multiple doses of acclidinium.^{18,19} In a subsequent study, which included patients with moderate to severe COPD, acclidinium displayed long-lasting bronchodilation and was well tolerated.²⁰ Acclidinium can be found in a fixed drug combination with formoterol known as Duaklir Pressair.

Umeclidinium (Incruse Ellipta) is a long-acting anticholinergic, developed by Theravance (San Francisco, California) and Glaxo-SmithKline (Brentford, UK) and approved by the FDA in May 2014, for once-daily maintenance treatment of airflow obstruction in patients with COPD. Incruse Ellipta is a DPI that should be used daily at the same time each day. Umeclidinium bromide has activity across multiple muscarinic receptors and exerts its bronchodilatory activity by competitively inhibiting the binding of ACh with muscarinic cholinergic receptors on airway smooth muscle (M₃). It demonstrates slow reversibility at the M₃ receptor, providing long duration of bronchodilation in the lungs.²¹

Umeclidinium bromide and vilanterol (Anoro Ellipta) is a combination agent providing 62.5 mcg of umeclidinium and 25 mcg of vilanterol—a long-acting anticholinergic and β agonist used to treat airflow limitations in COPD once daily. In a randomized, double-blind, placebo-controlled, parallel-controlled study of almost 1500 patients, Anoro Ellipta was found to provide greater improvements in lung function, health status, and dyspnea scores compared with the individual use of the drugs in the combination.²² Although the use of combination agents in respiratory care is common, not all patients need combination agents. The use of β agonists (see Chapter 6) and inhaled glucocorticoids (see Chapter 11) do present risks.

Clinical Pharmacology

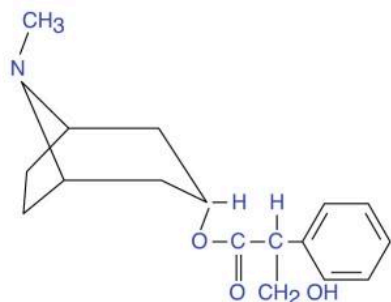
Structure–Activity Relationships

Chemical structures of the two naturally occurring belladonna alkaloids, atropine and scopolamine (also called *hyoscine*), are illustrated in Fig. 7.1. Atropine, including its sulfate (atropine sulfate), and scopolamine are tertiary ammonium compounds that differ from each other only by an oxygen atom bridging the carbon-6 and carbon-7 positions. Quaternary ammonium derivatives of atropine include atropine, ipratropium, and tiotropium. Another quaternary atropine derivative, which has been administered experimentally as a bronchodilator by aerosol, is glycopyrrolate (Robinul) (not shown in Fig. 7.1).

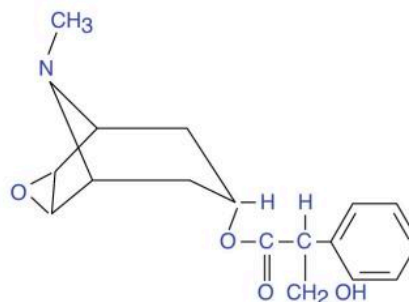
Tertiary ammonium forms, such as atropine sulfate or scopolamine, are easily absorbed into the bloodstream, distribute throughout the body, and in particular cross the blood–brain barrier to cause CNS changes. Quaternary ammonium forms (e.g., ipratropium, tiotropium, and glycopyrrolate) are fully ionized and poorly absorbed into the bloodstream or the CNS. As a result,

Anticholinergic (Parasympatholytic) Agents

Tertiary Ammonium Compounds

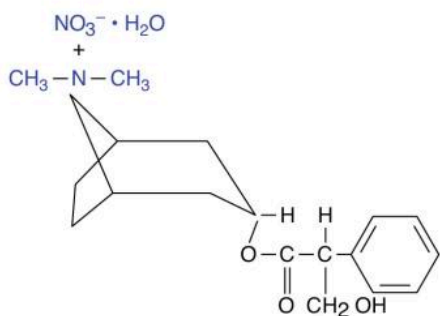


Atropine

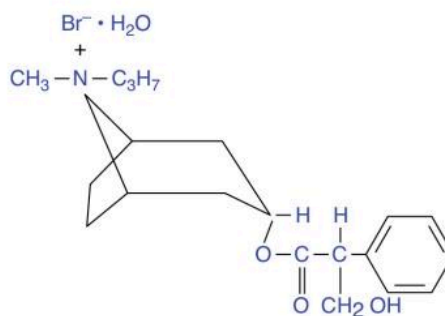


Scopolamine (Hyoscine)

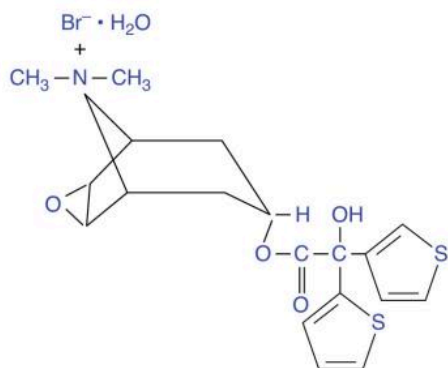
Quaternary Ammonium Compounds



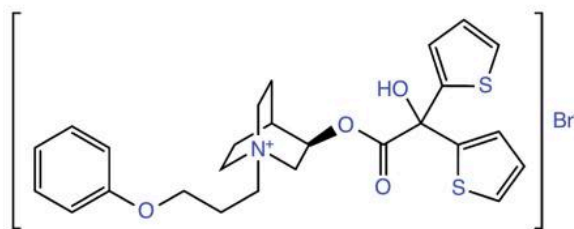
Atropine methylnitrate



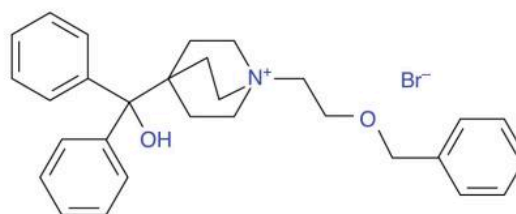
Ipratropium bromide



Tiotropium bromide



Acridinium bromide



Umeclidinium

• **Fig. 7.1** Chemical structures of anticholinergic (parasympatholytic) agents: tertiary compounds, such as atropine and scopolamine, and quaternary compounds, such as ipratropium, tiotropium, acridinium, and umeclidinium.

the systemic side effects seen with aerosol administration of the tertiary ammonium atropine sulfate do not occur or are minimal with a quaternary ammonium, such as ipratropium. Quaternary ammonium agents given by inhalation generally are poorly

absorbed from the lungs. They are not rapidly removed from the aerosol deposition site and do not cross the blood–brain barrier as atropine sulfate does, giving them a wider therapeutic margin in relation to side effects.

TABLE 7.2 Comparison of Cholinergic Antagonism (Antimuscarinic Effects) With Cholinergic Effects (Muscarinic Effects)

Cholinergic Effect	Anticholinergic Effect
Decreased heart rate	Increased heart rate
Miosis (contraction of iris, eye)	Mydriasis (pupil dilation)
Contraction (thickening) of lens, eye	Cycloplegia (lens flattened)
Salivation	Drying of upper airway
Lacrimation	Inhibition of tear formation
Urination	Urinary retention
Defecation	Antidiarrheal or constipation
Secretion of mucus	Mucociliary slowing
Bronchoconstriction	Inhibition of constriction

Pharmacologic Effects of Anticholinergic (Muscarinic Antagonist) Agents

The general effects of **cholinergic (muscarinic)** stimulation and the corresponding effects produced by anticholinergic (antimuscarinic) action are listed in [Table 7.2](#). Specific effects differ for tertiary and quaternary ammonium compounds because of their absorption differences, as previously outlined, for their structure–activity relationships. These effects and their differences are summarized in [Table 7.3](#) and discussed subsequently.

Tertiary Ammonium Compounds

Tertiary compounds include atropine sulfate, scopolamine, and hyoscyamine sulfate. They are well absorbed across mucosal surfaces and their effects increase with the size of the dose. Effects are summarized for these agents for the organ systems.

Respiratory Tract Effects. Atropine sulfate, a prototype tertiary compound, inhibits and reduces mucociliary clearance, as shown by Groth et al.²³ Atropine seems to block hypersecretion stimulated by cholinergic agonists in both the lower airway and the nose (upper airway) more than basal secretion.²⁴ Atropine relaxes airway smooth muscle, which is the basis for its use in asthma.

Central Nervous System Effects. Tertiary compounds cross the blood–brain barrier and produce dose-related effects. Small doses of 0.5 to 1.0 mg can cause effects that include restlessness, irritability, drowsiness, fatigue, or, alternatively, mild excitement. Increased doses can cause disorientation, hallucinations, or coma. Inhaled atropine has been reported to cause an acute psychotic reaction.^{25,26}

Eye Effects. Tertiary anticholinergic compounds given by inhalation distribute through the bloodstream and can affect vision. They block contraction of the iris to cause pupil dilation and paralyze the ciliary muscle of the lens to prevent thickening of the lens for near sight accommodation, causing blurred vision. These effects can increase intraocular pressure in glaucoma. Atropine-like agents are contraindicated in narrow-angle glaucoma.

Cardiac Effects. Atropine in small doses causes minor slowing of heart rate; larger doses increase heart rate through vagal blockade.

Gastrointestinal Effects. Anticholinergic agents generally cause dryness of the mouth as a result of inhibition of salivary

TABLE 7.3 Pharmacologic Effects of Tertiary Versus Quaternary Anticholinergic Agents Given by Inhaled Aerosol

	Tertiary (Atropine)	Quaternary (Ipratropium and Tiotropium)
Respiratory tract	Bronchodilation Decreased mucociliary clearance Blockage of hypersecretion	Bronchodilation Little or no change in mucociliary clearance Blockage of nasal hypersecretion
CNS	Altered CNS function (dose related)	No effect
Eye	Mydriasis Cycloplegia Increased intraocular pressure	Usually no effect*
Cardiac	Minor slowing of heart rate (small dose); increased heart rate (larger dose)	No effect
Gastrointestinal	Dry mouth, dysphagia; slows motility	Dry mouth
Genitourinary	Urinary retention	Usually no effect†

*Assumes aerosol is not sprayed into eye; use with caution in glaucoma.

†Use with caution in prostatic enlargement or urinary retention.

CNS, Central nervous system.

gland secretions, and atropine is used for this effect to reduce upper airway secretions before surgery and anesthesia or when reversing neuromuscular blockade (see [Chapter 18](#)). Larger doses can cause dysphagia. Gastrointestinal motility is slowed, an effect that is the basis for the inclusion of atropine in Lomotil, an antidiarrheal agent. Inhibition of gastrointestinal motility and emptying has been noted with normal doses of atropine given by aerosol to asthmatics.²⁷

Genitourinary Effects. Atropine-like agents can inhibit parasympathetic-controlled relaxation of the urinary sphincter. In men with prostate gland enlargement, this can produce acute urinary retention. Atropine-like drugs can predispose male patients to impotence because penile erection is also under parasympathetic control. Ejaculation is a sympathetic function.

Quaternary Ammonium Compounds

Quaternary compounds include the approved aerosol agent ipratropium, tiotropium, and glycopyrrolate. The following effects are discussed primarily for ipratropium, which is well known as an inhaled bronchodilator. Generally, quaternary ammonium compounds do not cross lipid membranes easily and do not distribute throughout the body when inhaled. Some agents, such as ipratropium, produce an anticholinergic effect at the site of delivery; with inhalation, this would be the nose or mouth and the upper and lower airway.

Respiratory Tract Effects. Ipratropium has minimal or no effect on mucociliary clearance or mucus viscosity despite the

fact that the aerosol is delivered topically to the airways. The drug causes bronchodilation by blocking cholinergic contractile action. In the nasal passages, however, ipratropium reduces hypersecretion, which is the basis for its use in rhinitis.

Central Nervous System Effects. Because quaternary compounds do not cross the blood–brain barrier, they do not cause CNS effects as the tertiary agents do.

Eye Effects. If ipratropium and other quaternary agents are not sprayed directly in the eye, there are no effects on intraocular pressure, pupil size, or lens accommodation when inhaled as aerosol drugs. Topical delivery to the eye can cause pupillary dilation (mydriasis) and lens paralysis (cycloplegia). Subjects using quaternary ammonium **muscarinic antagonist bronchodilators** (an agent that blocks effects of Ach) must be cautioned to protect their eyes from the aerosol drug.

Cardiac Effects. Ipratropium has minimal effects on heart rate and blood pressure when given as an inhaled aerosol drug. However, several meta-analyses have suggested that ipratropium and tiotropium may cause an increase in cardiovascular events. When other meta-analyses were conducted and reexamined, no incidence of cardiovascular involvement from inhaled anticholinergics was found. Currently no information has been conclusive in showing that these agents have any adverse effects on the cardiovascular system.²⁸

Gastrointestinal Effects. In most patients, inhaled ipratropium has little effect on gastrointestinal motility. A portion of the aerosol dose is swallowed, however, allowing exposure of the gastrointestinal tract to the drug. There has been a report of meconium ileus in an adult with cystic fibrosis receiving nebulized ipratropium.²⁹ Use of a reservoir device with MDI administration can reduce oropharyngeal impaction and the amount of swallowed drug.

Genitourinary Effects. When tested in men 50 to 70 years of age, ipratropium was found to have no effect on urinary function.³⁰

KEY POINT

Quaternary compounds, such as ipratropium, are fully ionized and less absorbed into body tissues compared with *tertiary compounds*, such as atropine sulfate. Consequently, side effects with quaternary compounds are localized to the site of drug exposure.

Mechanism of Action

In Chapter 5, the autonomic innervation of the airway is outlined; this consists of the traditional sympathetic and parasympathetic

branches and nonadrenergic, noncholinergic (NANC) inhibitory and excitatory branches. The sympathetic branch does not actually extend its fibers beyond the peribronchial ganglia or plexuses to the airway, although adrenergic receptors are present throughout the airway, especially in the periphery. Parasympathetic nerves enter the lung at the hila, deriving from the vagus, and travel along the airways. Parasympathetic postganglionic fibers terminate on or near the airway epithelium, submucosal mucous glands, smooth muscle, and probably mast cells. Parasympathetic innervation and muscarinic receptors are concentrated in the larger airways, although they are present from the trachea to the respiratory bronchioles.

In the normal airway, a basal level of bronchomotor tone is caused by parasympathetic activity. This basal level of tone can be abolished by anticholinergic agents, such as atropine, indicating it is mediated by Ach. Administration of **parasympathomimetic** (cholinergic) agents, such as methacholine (e.g., in bronchial provocation testing), can intensify the level of bronchial tone to the point of constriction in healthy subjects and more so in patients with asthma.

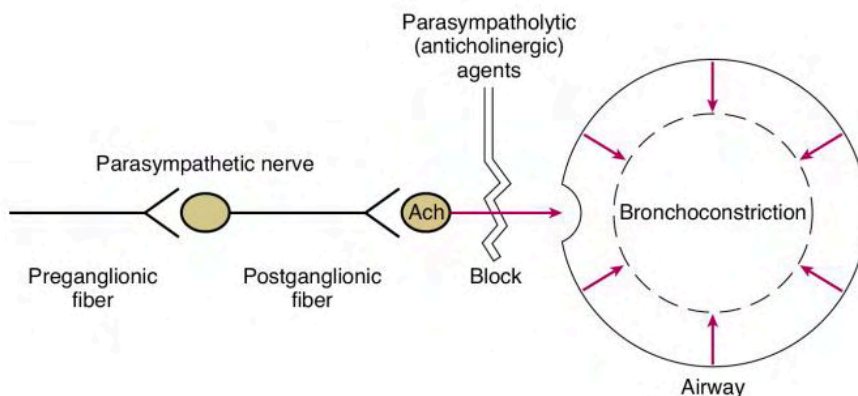
Cholinergic stimulation of muscarinic receptors on airway smooth muscle and submucosal glands causes contraction and release of mucus. Anticholinergic agents, such as atropine or ipratropium, are antimuscarinic; they competitively block the action of Ach at parasympathetic postganglionic effector cell receptors. Because of this action, anticholinergic agents block cholinergic-induced bronchoconstriction, as shown in Fig. 7.2.

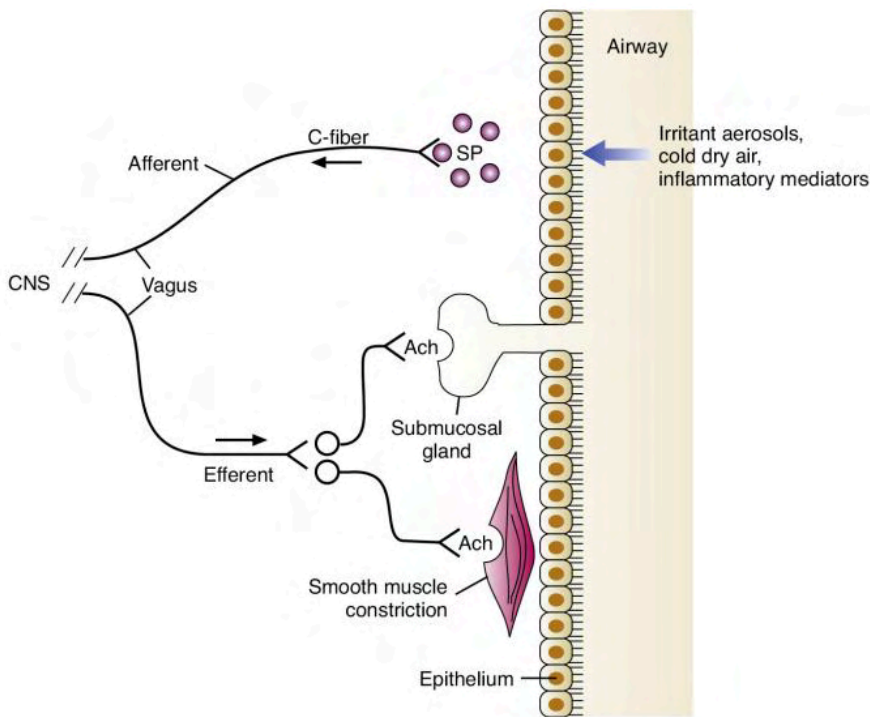
An important point to realize with use of a blocking agent, such as an **anticholinergic bronchodilator**, is that the effect seen depends on the degree of tone present that can be blocked. In healthy subjects, there is minimal airway dilation with an anticholinergic agent because there is only a basal or resting level of tone to be blocked. Variation in the clinical effect of such drugs is partially caused by variation in the degree of parasympathetic activity. One particular mechanism for parasympathetic activity in the lung is vagally mediated reflex bronchoconstriction, which is discussed in the next section.

CLINICAL CONNECTION

The anticholinergic agents ipratropium, aclidinium, glycopyrrolate, revefenacin, tiotropium, and umeclidinium are indicated for the treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). Ipratropium is indicated in the treatment of asthma exacerbation, and tiotropium is now indicated as add-on in the maintenance treatment of asthma.

• **Fig. 7.2** Conceptual overview of the action of anticholinergic (parasympatholytic) bronchodilating agents in preventing cholinergic-induced bronchoconstriction. Ach, Acetylcholine.





• **Fig. 7.3** Mechanism of vagally mediated reflex bronchoconstriction induced by nonspecific stimuli on sensory C-fibers. *Ach*, Acetylcholine; *CNS*, central nervous system; *SP*, substance P.

Vagally Mediated Reflex Bronchoconstriction

A portion of the bronchoconstriction seen in COPD may be caused by a mechanism of vagally mediated reflex innervation of airway smooth muscle (Fig. 7.3). Sensory C-fiber nerves respond to various stimuli, such as irritant aerosols (hypotonic or hypertonic), cold air and high airflow rates, cigarette smoke, noxious fumes, and mediators of inflammation, such as histamine. When activated, they produce an afferent nerve impulse to the CNS, which results in a reflex cholinergic efferent impulse to cause constriction of airway smooth muscle and release of secretion from mucous glands, as well as cough.

Because atropine and its derivatives are competitive inhibitors of ACh at the neuroeffector junction, such antagonists should block parasympathetic reflex bronchoconstriction. Atropine has been shown to inhibit exercise-induced asthma and psychogenic bronchospasm and bronchoconstriction caused by β blockade or cholinergic agents. Application of a topical anesthetic, such as 4% lidocaine by aerosol, to the large airways has also inhibited reflex bronchoconstriction by blocking the sensory irritant receptors in the epithelial lining.

Changes in the airway may also sensitize the subepithelial cough receptors, making them more responsive to lower thresholds of stimulation. This sensitization is often seen during colds that involve lung congestion. Lung inflation during a deep breath stimulates the cough receptors, resulting not only in coughing but also increased bronchomotor tone. It has been suggested that greater bronchial reactivity in patients with asthma or those with COPD may be caused by mucosal edema and deformation of airway tissue, which increases the sensitivity of these receptors in response to irritants. Several reviews of cholinergic mechanisms of airway obstruction have been published.^{31–35}

TABLE 7.4 Muscarinic Receptor Subtypes: G Proteins and Effector Systems

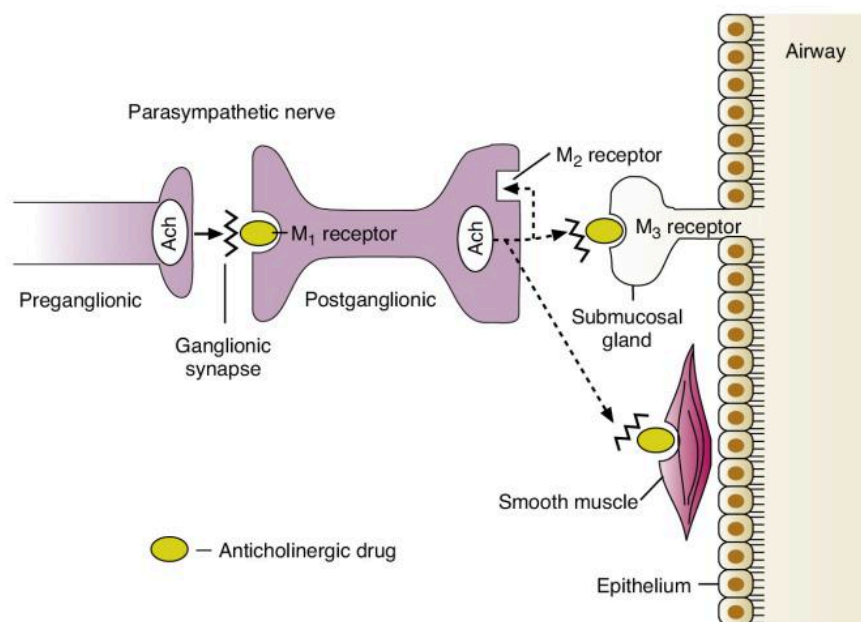
Receptor	G Protein	Effector
M ₁	G _q	Phospholipase C
M ₂	G _i	Adenylyl cyclase (decreases)
M ₃	G _q	Phospholipase C
M ₄	G _i	Adenylyl cyclase (decreases)
M ₅	G _q	Phospholipase C leads to an increase

Muscarinic Receptor Subtypes

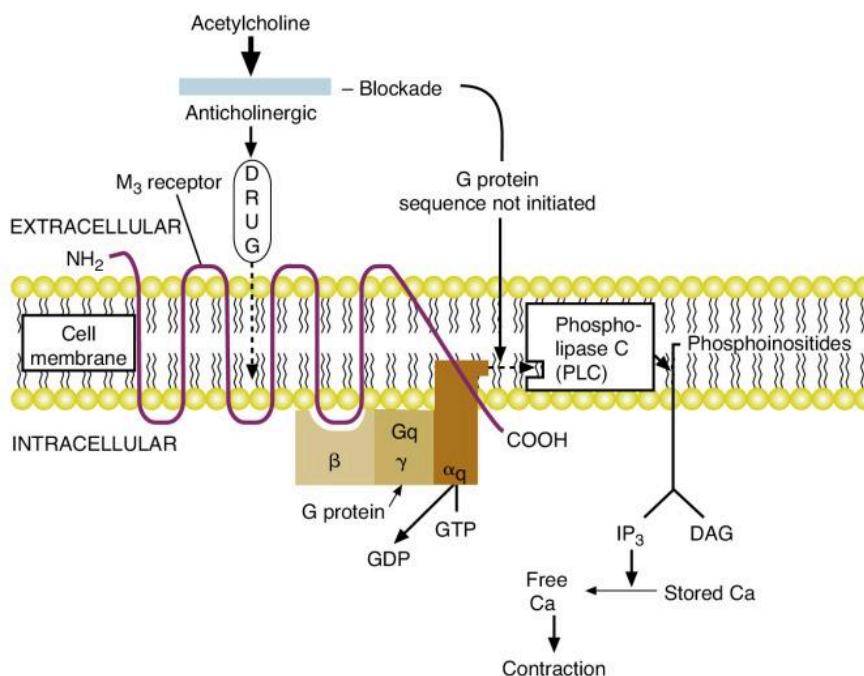
Anticholinergic agents cause bronchodilation by blocking M₁ receptors at the parasympathetic ganglia, which facilitate cholinergic neurotransmission and bronchoconstriction, and M₃ receptors on airway smooth muscle, which cause bronchoconstriction. Muscarinic receptor subtypes are reviewed in Chapter 5 and are illustrated for the lung in Fig. 7.4. M₁ receptors on the postganglionic parasympathetic neuron facilitate cholinergic nerve transmission, leading to release of ACh. ACh stimulates M₃ receptor subtypes on airway smooth muscle and submucosal glands, causing contraction of smooth muscle and exocytosis of secretion from the mucous gland. Additionally, the M₂ receptor subtype at cholinergic nerve endings inhibits further ACh release from the postganglionic neuron.

M₃ receptors are G protein–linked receptors (see Chapters 2 and 5). Table 7.4 lists the various muscarinic receptor subtypes and their G proteins, along with their effector enzymes. Stimulation of

• **Fig. 7.4** Identification and location of muscarinic receptor subtypes M_1 , M_2 , and M_3 in the vagal nerve, submucosal gland, and bronchial smooth muscle in the airway, showing nonspecific blockade by anticholinergic drugs, such as ipratropium. *Ach*, Acetylcholine.



• **Fig. 7.5** Illustration of the M_3 receptor as a G protein-linked receptor, showing the G_q protein; its effector system, phospholipase C (PLC); and the mechanism of smooth muscle constriction, which is blocked by an anticholinergic agent preventing stimulation of the M_3 receptor. *DAG*, Diacylglycerol; *GDP*, guanosine diphosphate; *GTP*, guanosine triphosphate; *IP₃*, inositol triphosphate.



the M_3 receptor subtype activates a G_q protein, which activates phospholipase C (PLC). PLC causes the breakdown of phosphoinositides into inositol triphosphate (IP_3) and diacylglycerol (DAG); this ultimately leads to an increase in the cytoplasmic concentration of free calcium and smooth muscle contraction or gland exocytosis. As shown in Fig. 7.5, the competitive blockade of M_3 receptors by anticholinergic agents prevents this sequence. The blockade of M_1 receptor subtypes by anticholinergic agents also inhibits nerve transmission by Ach at the ganglionic synapse. Both ipratropium and tiotropium also block the M_2 receptor. This receptor inhibits continued release of Ach. As a result, blockade of the M_2 receptor can enhance Ach release, possibly counteracting the bronchodilator effect of M_3 receptor blockade. As noted in the

discussion of ipratropium and tiotropium, tiotropium has selective affinity for M_1 and M_3 receptors because it dissociates much more rapidly from the M_2 receptor and remains bound to the M_1 and M_3 subtypes.

The use of such agents as ipratropium for allergic and nonallergic rhinitis is based on the parasympathetic control of submucosal glands in the nasal mucosa. Ach stimulates muscarinic receptors in the nose, where approximately 55% are M_3 receptors, and the rest are M_1 receptors.³⁶ M_2 receptors were not identified in human nasal mucosa in an autoradiographic study by Okayama et al.³⁷ Blockade of muscarinic M_1 and M_3 receptors on submucosal nasal glands by ipratropium given as a nasal spray prevents gland secretion and rhinitis.

CLINICAL CONNECTION

Blockade of M_1 and M_3 receptors in the nasal passages prevents gland secretion and rhinitis.

Adverse Effects

It has been stated that the safety profile of quaternary ammonium antimuscarinic bronchodilators (e.g., ipratropium and tiotropium) is superior to that of β agonists, particularly with regard to cardiovascular effects.⁹ Changes in electrocardiography (ECG) measurements, blood pressure, or heart rate are not usually seen. There is no worsening of ventilation–perfusion abnormalities in COPD, which would otherwise cause an increase in hypoxemia. Tolerance to bronchodilation and loss of bronchial protection have not been observed. The lack of these effects is caused by the poor absorption and systemic distribution of quaternary compounds, such as ipratropium. Cugell³⁸ provided a detailed review of the clinical pharmacology and toxicology of ipratropium.

The side effects seen with the MDI and small volume nebulizer (SVN) formulations of ipratropium, the agent with the most clinical experience, are primarily related to the local, topical delivery to the upper and lower airway with inhalation. Similar side effects would be expected with other antimuscarinic agents, such as tiotropium. The most common side effect seen with this class of bronchodilator is dry mouth. Possible side effects are listed in [Box 7.1](#). The SVN solution has also been associated with additional side effects in a few patients, including pharyngitis, dyspnea, flulike symptoms, bronchitis, and upper respiratory infection. The amount of drug in the nebulizer dose is greater than

• **BOX 7.1** Side Effects Seen With Anticholinergic Aerosol Ipratropium*

MDI and SVN (Common)

- Dry mouth
- Cough

MDI (Occasional)

- Nervousness
- Irritation
- Dizziness
- Headache
- Palpitation
- Rash

SVN (Occasional)

- Pharyngitis
- Dyspnea
- Flulike symptoms
- Bronchitis
- Upper respiratory infections
- Nausea
- Occasional bronchoconstriction
- Eye pain
- Urinary retention (less than 3%)

*Side effects were reported in a small percentage (<3% to 5%) of patients.

Precautions: Use with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, bladder neck obstruction, constipation, bowel obstruction, or tachycardia.

MDI, Metered dose inhaler; SVN, small volume nebulizer.

10 times that in the MDI dose (500 mcg versus 40 mcg). If the patient receives approximately 10% of an inhaled aerosol to the lung, a much larger dose is given with an SVN. The orally swallowed portion would also be proportionately higher. Systemic side effects, such as tachycardia, palpitations, urinary hesitancy, constipation, blurred vision, and increased ocular pressure, are less likely with quaternary agents, such as ipratropium, tiotropium, aclidinium, or umeclidinium, than with tertiary agents, such as atropine. Although ipratropium is not contraindicated in subjects with prostatic hypertrophy, urinary retention, or glaucoma, the drug should be used with caution and adequate evaluation for possible systemic side effects in these subjects.

The eye must be protected from aerosol drug exposure resulting from accidental spraying or during nebulizer delivery. Blockade of muscarinic receptors causes mydriasis by blocking the sphincter muscle of the iris and inhibits the ciliary muscle of the lens, preventing lens thickening (accommodation). As the iris dilates outward, the lens remains flattened, and drainage of intraocular aqueous humor is reduced. In patients with narrow-angle glaucoma, intraocular pressure can increase. Because many patients with COPD are older, narrow-angle glaucoma may be present more commonly. Subjects using quaternary ammonium antimuscarinic bronchodilators must be informed of this hazard and should use proper aerosol inhalation technique. A holding chamber should be used with MDI administration. With nebulizer delivery, the mouthpiece should be kept in the mouth and a reservoir tube attached to the expiratory side of the T mouthpiece to vent aerosol away from the face. The ideal nebulizer would be a dosimetric device with no ambient exposure from the device on exhalation. If the nebulizer solution is delivered by facemask (which is not recommended), the eyes should be closed or covered to prevent drug exposure. Because of the greater risk of eye exposure with a nebulizer, especially disposable, constant-output devices, an MDI with a holding chamber is recommended for delivery of this class of bronchodilator.

CLINICAL CONNECTION

The most common side effects with quaternary ammonium antimuscarinic bronchodilators are dry mouth and perhaps cough caused by the aerosol particles.

CLINICAL CONNECTION

Direct spraying in the eye must be avoided to prevent ocular effects. Patients with chronic obstructive pulmonary disease (COPD) can show a greater response in reversibility of airflow obstruction with an anticholinergic agent than with a β agonist.

Clinical Application

Anticholinergic (antimuscarinic) aerosols have been investigated for use with asthma and with COPD. [Table 7.5](#) compares the general effects seen with anticholinergic bronchodilators and β -adrenergic bronchodilators.

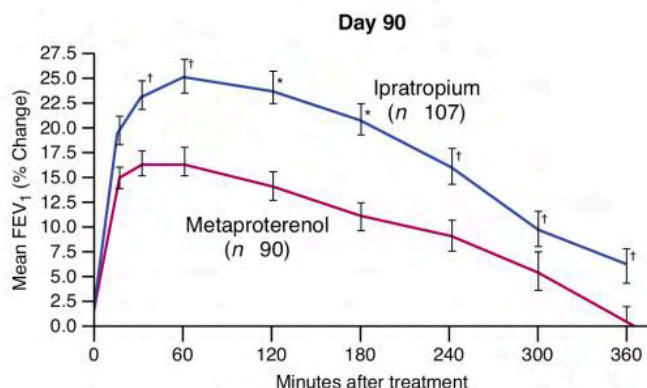
Use in Chronic Obstructive Pulmonary Disease

Antimuscarinic agents were found to be more potent bronchodilators than β -adrenergic agents in bronchitis/emphysema, and this

TABLE 7.5 Comparison of Effects for Anticholinergic and β -Adrenergic Bronchodilators

	Anticholinergic	β Agonist
Onset	Slightly slower	Faster
Time to peak effect	Slower	Faster
Duration	Longer	Shorter
Tremor	None	Yes
Decrease in PaO_2	None	Yes
Tolerance	None	Yes
Site of action	Larger, central airways	Central and peripheral airways

PaO_2 , Arterial oxygen pressure.



• **Fig. 7.6** Effect of the β -agonist metaproterenol and the anticholinergic ipratropium on forced expiratory volume in 1 second (FEV_1) in patients with chronic obstructive pulmonary disease after 90 days of treatment (* $P < 0.01$; † $P < 0.05$). (From Tashkin, D. P., Ashutosh, K., Bleecker, E. R., et al. [1986]. Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease: a 90-day multicenter study, *American Journal of Medicine*, 81[Suppl 5A], 59. From Excerpta Medica, Inc.)

is likely to be their primary clinical application. This difference is illustrated in Fig. 7.6 with data from Tashkin et al.³⁹ In the 90-day, multicenter study, the investigation compared 40 mcg of ipratropium with 1.5 mg of metaproterenol, both given by MDI, in a population of patients with COPD. Explanations for the superiority of anticholinergic action in COPD are debated but may relate to the complicated, inflammatory, noncholinergic pathways seen in asthma, especially resulting from stimuli mentioned previously in the section on vagally mediated reflex bronchoconstriction. Conversely, the pathology of COPD may reveal the reason for the superior effect of anticholinergic drugs compared with β -adrenergic drugs. Ipratropium has been approved by the FDA specifically for use in the treatment of COPD, although the drug is also prescribed for treatment of asthma.

Rennard et al.⁴⁰ analyzed data from clinical trials comparing ipratropium with a β agonist. Their analysis showed that use of ipratropium over the 90-day interval tested was associated with

improved baseline lung function and response to acute bronchodilator use. Subjects using β agonists over the same period had little change in baseline lung function and a small decrease in airway response to acute bronchodilator treatment.

The addition of numerous long-acting antimuscarinic agents (LAMAs) have been developed to treat COPD. All agents approved by the FDA are available as once or twice daily with similar safety and efficacy.^{7–12} Beeh et al.⁴¹ reported that an inhaled dose of a LAMA once per day improved lung function and reduced exacerbations in patients with COPD of different severities. Adams et al.⁴² also found improvement in lung function and dyspnea in patients with COPD who had not been treated with maintenance therapy previously. The prolonged effect may also be useful in controlling nocturnal asthma symptoms, where cholinergic mechanisms seem to increase airway tone.⁴³

Current COPD guidelines do not mandate the use of any one specific bronchodilator.^{44,45} It is noted, however, that the use of a short-term β_2 agonist and an anticholinergic, such as ipratropium, improves FEV_1 in patients with COPD.⁴⁵ The use of a long-term anticholinergic, such as tiotropium, revefenacin, aclidinium, glycopyrrolate, or umeclidinium, improves the health of patients with COPD.

Use in Asthma

Anticholinergic (antimuscarinic) agents, such as ipratropium, do not have a labeled indication for asthma in the United States. Current asthma guidelines state that ipratropium may have some additive benefit when given with inhaled β agonists.^{46,47} Antimuscarinic bronchodilators are not clearly superior to β -adrenergic agents in treating asthma. Antimuscarinic and β -adrenergic agents have an approximately equal effect on flow rates in many patients. These agents may be especially useful in the following applications when prescribed for patients with asthma⁴⁸:

- Nocturnal asthma, in which the slightly longer duration of action may protect against nocturnal deterioration of flow rates⁴⁹
- Psychogenic asthma, which may be mediated through vagal parasympathetic fibers
- Patients with asthma, as well as glaucoma, angina, or hypertension, requiring treatment with β -blocking agents
- As an alternative to theophylline in patients with notable side effects from that drug
- Acute, severe episodes of asthma not responding well to β agonists

A large, randomized controlled study by Qureshi et al.⁵⁰ in 434 children (ages 2 to 8 years) with acute moderate to severe asthma found that the overall rate of hospitalization was reduced with the addition of inhaled ipratropium to nebulized albuterol. However, the most striking effect on admission was seen in children with severe asthma (peak expiratory flow <50% predicted). A meta-analysis of the addition of anticholinergic bronchodilators to β agonists in children and adolescents, conducted by Plotnick and Ducharme,⁵¹ concluded that adding multiple doses of antimuscarinic bronchodilators to β_2 agonists was safe,⁴⁵ improved lung function, and may help avoid hospital admission in 1 of 11 treated patients. Multiple doses should be preferred to single doses of antimuscarinic agents. However, new studies have shown the use of tiotropium as an effective add-on treatment for asthma in patients as young as age 6 years.^{13,14}

Combination Therapy: β -Adrenergic and Anticholinergic Agents in Chronic Obstructive Pulmonary Disease

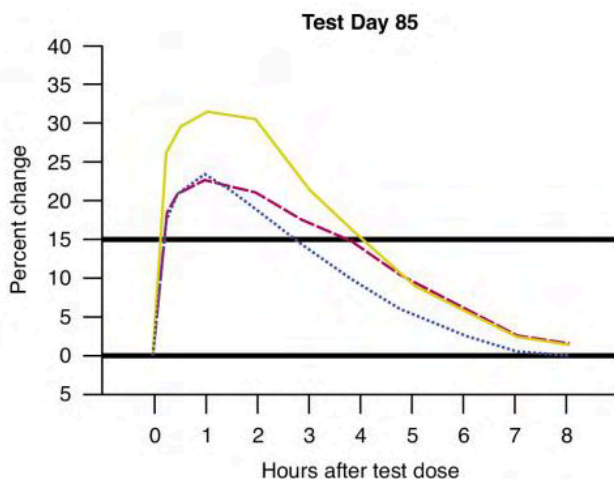
Theoretically, a combination of β -adrenergic and anticholinergic agents should offer advantages in the treatment of COPD (as well as asthma), based on the following considerations:

- Complementarity of sites of action exists, with anticholinergic effect seen in the more central airways and β -agonist effect in the smaller, more peripheral airways.
- Mechanisms of action from anticholinergic and β -adrenergic agents are separate and complementary.

Pharmacokinetics of shorter-acting agents (albuterol or ipratropium) in the two classes of bronchodilator are complementary; the effects of β agonists peak sooner but also terminate sooner, whereas the effects of anticholinergics tend to peak more slowly and last longer. This consideration is irrelevant, however, with longer-acting agents in both classes, such as salmeterol, formoterol, arformoterol, indacaterol, vilanterol, tiotropium, glycopyrrolate, revefenacin, aclidinium, and umeclidinium.

Additive Effect of β Agonists and Anticholinergic Agents

Conflicting results have been found regarding whether the bronchodilator effect of β agonists is increased by adding an anticholinergic agent, in either COPD or asthma.^{52–56} However, a large study—the Combivent Inhalation Aerosol Study Group,⁵ a well-controlled study conducted over 85 days with 462 patients at 24 centers on patients with stable COPD—showed superior efficacy of the combination therapy of ipratropium and albuterol compared with either agent alone. Fig. 7.7 compares this study of ipratropium plus albuterol versus albuterol or ipratropium alone on the percentage change in FEV₁. The mean *peak* increases in FEV₁ were 31% to 33% for combined drug therapy compared with 24% to 25% for ipratropium alone and 24% to 27% for albuterol alone. Flow rates were significantly better on all test days. Symptom scores did not differ among the three groups, however.



• **Fig. 7.7** Percentage change in forced expiratory volume in 1 second (FEV₁) on test day 85, for combined ipratropium and albuterol compared with either drug alone, in patients with chronic obstructive pulmonary disease (COPD). Dotted line, Albuterol; dashed line, ipratropium; solid line, ipratropium plus albuterol. (From COMBIVENT Inhalation Aerosol Study Group. [1994]. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone: an 85-day multicenter trial, *Chest*, 105, 1411.)

As a large, well-designed study, these results support combination anticholinergic and β -agonist therapy in COPD.

Sequence of Administration

The order in which a β_2 agonist and an anticholinergic are administered via an MDI has been debated. Because an anticholinergic bronchodilator acts in the central, larger airways, some practitioners argue that it should be given *before* the β_2 agonist. No data have been published to support this sequence, however. The β_2 agonist is often given first, and this can be rationalized for two reasons: (1) a β_2 agonist has a more rapid onset of action than an anticholinergic bronchodilator; and (2) β_2 receptors are distributed in large and small airways. The order of administration is probably not important. Combination products, such as Combivent ipratropium and albuterol, make the order of administration a moot point.

Most discussion and clinical use of β_2 agonists and anticholinergics have centered on agents with shorter duration. Other combination agents have included long-acting β_2 agonists and inhaled corticosteroids. The use of long-acting β_2 agonists and long-acting anticholinergics may be as effective as shorter-acting agents. In a study of tiotropium and formoterol, it was found that lung function improved with the combination compared with the agents given as monotherapy in patients with stable COPD.⁵⁷ Another study of patients with moderate to severe COPD found that a combination of tiotropium and formoterol increased forced vital capacity (FVC) and FEV₁ more compared with the agents delivered alone.⁵⁸

Two of the largest, long-term drug trials for COPD—Towards a Revolution in COPD Health (TORCH) and Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT)—have provided insight into the prescribing practice of medications used to treat COPD. Miravittles and Anzueto⁵⁹ reviewed both studies. The main conclusion concerning combination agents is that the long-term agents tiotropium and salmeterol, with the addition of an inhaled corticosteroid, improve lung function and may arrest the progression of COPD. The use of these agents is being termed “triple therapy,” suggesting improvement when all three are used in combination.^{60–62} Currently, Trelegy Ellipta is available as a fixed-dose DPI that contains all three agents (see Chapter 11).

RESPIRATORY CARE ASSESSMENT OF ANTICHOLINERGIC BRONCHODILATOR THERAPY

Before Treatment

- Assess effectiveness of drug therapy based on the indication for the aerosol agent: The presence of reversible airflow results from primary bronchospasm or obstruction secondary to an inflammatory response or secretions, either acute or chronic.
- Monitor flow rates using bedside peak flow meters, portable spirometry, or laboratory reports of pulmonary function: Before-and-after bronchodilator studies performed with a β agonist may not reliably predict response to an anticholinergic (antimuscarinic) agent, such as ipratropium.
- Perform respiratory assessment: Breathing rate and pattern and breath sounds should be assessed by auscultation, before and after treatment.
- Assess pulse before, during, and after treatment.

During Treatment and Short Term

- Assess patient's subjective reaction to treatment for any change (positive or negative) in breathing effort or pattern.
- Assess arterial blood gases or pulse oximeter saturation, as needed, for acute states with COPD or asthma to monitor changes in ventilation and gas exchange (oxygenation).

Long Term

- Monitor pulmonary function studies of lung volumes, capacities, and flows.
- Instruct and then verify correct use of aerosol delivery device (SVN, MDI, reservoir, DPI). Emphasize that the eye must be protected from aerosol sprays. Instruct patients in use, assembly, and especially cleaning of aerosol inhalation devices.
- For long-acting antimuscarinic bronchodilators:
 - Assess ongoing lung function, including predose FEV₁, over time.
 - Assess amount of concomitant β -agonist use and nocturnal symptoms.
 - Assess number of exacerbations, unscheduled clinic visits, and hospitalizations.
 - Assess days of absence because of symptoms.

General Contraindications

- Anticholinergic bronchodilators generally are safe. However, regular, long-term use of short-acting and long-acting agents should be regularly assessed, especially if agents are used in combination with other agents.
- Use of anticholinergic bronchodilator therapy in patients with vision problems, such as glaucoma, should be closely monitored.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What was the first FDA-approved anticholinergic bronchodilator for aerosol inhalation?
2. List all FDA-approved long-acting anticholinergic combination product(s) on the market.
3. What is the usual recommended dose of ipratropium delivered by MDI and by SVN?
4. Identify a long-acting anticholinergic bronchodilator and give its duration of action.
5. What is the usual clinical indication for use of an anticholinergic bronchodilator, such as ipratropium?
6. Which disease state—asthma or COPD—may show greater response to an anticholinergic bronchodilator rather than a β agonist?
7. With which type of anticholinergic agent are you more likely to observe systemic side effects: tertiary ammonium compounds or quaternary ammonium compounds?
8. What are the most common side effects seen with inhaled ipratropium and tiotropium?
9. Can ipratropium be used with subjects who have glaucoma?
10. Can ipratropium be alternated with or combined with a β agonist in the treatment of COPD and asthma?
11. What precautions should you observe if administering ipratropium by SVN?
12. What is the clinical indication for the use of an anticholinergic intranasal spray?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

Logan O'Connor, age 66 years, is a well-educated, retired middle-level manager for a major film company. He is referred to a pulmonologist for his complaint of shortness of breath. On interview, Mr. O'Connor states that he has increasingly noticed exertional dyspnea with mild physical activity over the past few months. With questioning, he admits to occasional social alcohol intake of either one or two beers or a couple of mixed drinks several times a week. He has been happily married to the same woman since he was 24 years of age. He also admits to regular cigarette smoking of about one pack a day since he was 20 years of age. He leads a sedentary life, with no physical exercise. He states that he does have a chronic cough, which is worse in the morning, although he denies much productivity. He appears to be well nourished and is articulate, and his color is good. No cyanosis or use of accessory muscles at rest is noted.

Physical examination reveals very mild digital clubbing, a slightly increased anteroposterior (AP) diameter, diminished and distant breath sounds bilaterally with some rhonchi, mildly hyperresonant percussion notes, no jugular venous distention upright or supine, and no peripheral edema. His vital signs are as follows: blood pressure (BP) 146/90 mm Hg, temperature (T) 37.2°C, pulse (P) 88 beats/min, respiratory rate (RR) 16 breaths/min with no laboring. His arterial blood gas (room air) results are as follows: pH 7.40, arterial carbon dioxide pressure (PaCO₂) 42.5 mm Hg, arterial oxygen pressure (PaO₂) 62 mm Hg, base excess 1.9 mEq/L, and hemoglobin (Hgb) 14.5 g/dL.

His pulmonary function results are as follows:

Observed	% Predicted
Forced vital capacity (FVC), 2.98 L	74
Forced expiratory volume in 1 second (FEV ₁), 1.94 L	60
FEV ₁ /FVC	65 (Calculated)
Residual volume/total lung capacity (RV/TLC)	42 (Calculated)
Diffusing capacity of the lung for carbon monoxide (DLCO), 18.4 (mL/min/mm Hg)	70

Mr. O'Connor's chest radiograph (posteroanterior lateral) shows some loss of lung markings, mild flattening of the hemidiaphragms, and increased AP diameter. His electrolytes and white blood cell count are normal.

His chief complaint, smoking history, physical findings, and laboratory results all indicate early manifestations of chronic obstructive pulmonary disease (COPD). He is mildly hypoxemic at rest (PaO₂, 62 mm Hg), but his acid-base status is normal. Moderate airflow obstruction is present as evidenced by the FEV₁ of 1.94 L, FEV₁/FVC of 65%, and increased RV/TLC ratio. Gas exchange is impaired, as seen in the below-normal DLCO. There is no evidence of cardiac failure or acute exacerbation at this time. His diagnosis is COPD with mixed bronchitis and emphysema.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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Xanthines

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CHAPTER OUTLINE

Clinical Indications for the Use of Xanthines

- Use in Asthma
- Use in Chronic Obstructive Pulmonary Disease
- Use in Apnea of Prematurity

Specific Xanthine Agents

General Pharmacologic Properties

- Structure–Activity Relationships
- Proposed Theories of Activity
 - Inhibition of Phosphodiesterase*
 - Antagonism of Adenosine*
 - Catecholamine Release*

Titrating Theophylline Doses

- Serum Levels of Theophylline
- Dosage Schedules
- Theophylline Toxicity and Side Effects
- Factors Affecting Theophylline Activity

Clinical Uses of Theophylline

- Use in Asthma*
- Use in Chronic Obstructive Pulmonary Disease*

Nonbronchodilating Effects of Theophylline

- Respiratory Muscle Strength*
- Respiratory Muscle Endurance*
- Central Ventilatory Drive*
- Cardiovascular Effects*
- Antiinflammatory Effects*

Use in Apnea of Prematurity

Respiratory Care Assessment of Xanthines

- Before Treatment
- During Treatment and Short Term
- Long Term
- General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define xanthine
2. List all available xanthines used in respiratory therapy
3. Differentiate between the clinical indications of xanthines
4. Differentiate between the uses of xanthines
5. Discuss the proposed theories of activity for xanthines
6. Discuss adverse effects and toxicity of xanthines
7. Be able to assess xanthine therapy clinically

KEY TERMS AND DEFINITIONS

Alkaloids Group of alkaline substances taken from plants, which react with acids to form salts (e.g., theophylline).

Methylxanthines Chemical group of drugs derived from xanthines. There are three methylated (CH_3) xanthines: caffeine, theophylline, and theobromine.

Phosphodiesterase (PDE) Group of enzymes that change intracellular signaling.

This chapter reviews the pharmacology of the xanthine drugs, such as theophylline. Theophylline traditionally has been used to treat patients with asthma and chronic obstructive pulmonary disease (COPD) in stable and acute phases. The mechanism of action of xanthines is unclear, and their clinical use in asthma and COPD has been relegated to second- or third-line agents, although this remains an issue of debate.

KEY POINT

Theophylline is a member of the methylxanthine group of drugs.

Clinical Indications for the Use of Xanthines

KEY POINT

Clinical uses of theophylline include the management of asthma, chronic obstructive pulmonary disease (COPD), and apnea of prematurity in neonates.

Theophylline has traditionally been used in the management of asthma and COPD. Theophylline and caffeine have been used to treat apnea of prematurity. Theophylline was used as a diuretic but now is obsolete. Although theophylline is usually classified as a bronchodilator, it has a relatively weak bronchodilating effect compared with β_2 agonists. Its therapeutic action in asthma and COPD may occur by other means, such as stimulation of the ventilatory drive or direct strengthening of the diaphragm. Any of these actions could result in the clinical outcome of improved ventilatory flow rates; this is discussed later in the section “Clinical Uses of Theophylline.”

Use in Asthma

The National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group notes that sustained-release theophylline is indicated as an alternative for maintenance (step 2) therapy of mild, persistent asthma and higher in patients older than 5 years of age and is listed as an alternative in step 3 and higher for patients older than 5 years of age in combination with an inhaled corticosteroid (ICS). Sustained-release theophylline is considered a less-preferred alternative to low-dose ICS, cromolyn-like agents, or antileukotrienes as second-line maintenance drug therapy in stable asthma. Theophylline is not recommended in the guidelines for children younger than 5 years of age or for any person with acute exacerbation of asthma.¹ Global Initiative for Asthma (GINA) does not recommend the use of theophylline due to weak efficacy and side effects from its narrow therapeutic index.²

Use in Chronic Obstructive Pulmonary Disease

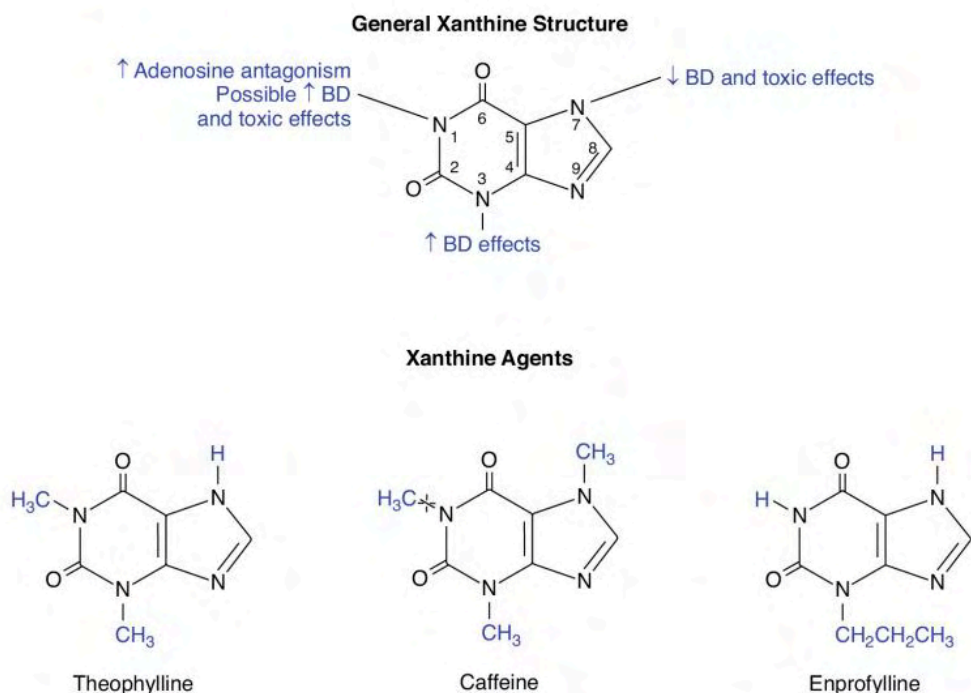
Current guidelines for the treatment of stable COPD state that bronchodilators are central to symptom management. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that inhaled bronchodilators are preferred when available. Theophylline is considered effective in COPD but, because of potential toxicity, is recommended as an alternative.³ Barr et al.⁴ conducted a meta-analysis on the use of xanthines for the treatment of COPD exacerbations. Their findings suggested that xanthines should not be used in the treatment of COPD exacerbations. In randomized controlled trials, intravenous aminophylline has not shown any significant benefit over β_2 agonists and anticholinergic therapy for patients with COPD.^{5,6}

Use in Apnea of Prematurity

If pharmacologic therapy is needed to stimulate breathing in apnea of prematurity, methylxanthines are considered the first-line agents of choice. Theophylline has been used most extensively, but Bhatia⁷ suggested that caffeine citrate may be the agent of choice. Caffeine citrate penetrates cerebrospinal fluid (CSF) better and has a higher therapeutic index with fewer side effects compared with theophylline. Caffeine citrate (Cafcit) has been approved for administration either intravenously or orally.

Specific Xanthine Agents

Theophylline is related chemically to the natural metabolite xanthine, which is a precursor of uric acid. Fig. 8.1 shows the general xanthine structure and the structures of theophylline (1,3-dimethylxanthine), caffeine (1,3,7-trimethylxanthine), and enprofylline. Because of their methyl attachments, these agents are often referred to as **methylxanthines**. Another xanthine is theobromine. All three agents are found as **alkaloids** in plant species. Caffeine is



• **Fig. 8.1** Effect of attachments at various sites on the xanthine molecule and comparative illustration of the structures of theophylline, caffeine, and enprofylline. BD, Bronchodilation.

TABLE 8.1 Xanthine Derivatives Used as Bronchodilators in Obstructive Airways Diseases, With Selected Brand Names and Available Formulations

Xanthine Derivative	Brand Names	Formulations
Theophylline	Elixophyllin, Theo-24, Generic	Tablets, capsules, syrup, elixir, extended-release tablets, capsules, injection

found in coffee beans and kola nuts. Caffeine and theophylline are contained in tea leaves, and caffeine and theobromine are found in cocoa seeds or beans. Historically, these natural plant substances have been used as brews for their stimulant effect.

Table 8.1 lists theophylline, brand names, and available formulations.

General Pharmacologic Properties

CLINICAL CONNECTION

Xanthines generally have *stimulant* properties, exemplified by the xanthine caffeine. Other effects of this class of drug include diuresis and smooth muscle relaxation (e.g., bronchodilation).

The xanthine group has the following general physiologic effects in humans:

- Central nervous system (CNS) stimulation
- Cardiac muscle stimulation
- Diuresis
- Bronchial, uterine, and vascular smooth muscle relaxation
- Peripheral and coronary vasodilation
- Cerebral vasoconstriction

Some of the effects seen with xanthines are well known to individuals who drink caffeinated beverages (e.g., coffee, colas, and tea). Coffee, in particular, can be used for the CNS stimulatory effect to remain awake. The diuretic effect after drinking coffee or cola is also well known. Caffeine or theophylline can also cause tachycardia, and the cerebral vasoconstricting effect has been used to treat migraine headaches. A special agent intended for this use is Cafegot, each tablet of which contains 100 mg of caffeine and 1 mg of ergotamine tartrate.

Caffeine and theophylline differ in the intensity of the effects listed previously. These differences are summarized in Table 8.2. Caffeine has more CNS-stimulating effect compared with theophylline, and this includes ventilatory stimulation. In clinical use, theophylline is generally classified as a bronchodilator because of the relaxing effect on bronchial smooth muscle.

Structure–Activity Relationships

Fig. 8.1 illustrates the general xanthine structure and the effect of attachments at various sites on the molecule. Also, the chemical structure of theophylline is shown. The methyl attachments at the nitrogen-1 and nitrogen-3 positions for theophylline enhance its bronchodilating effect and its toxic side effects, which are discussed later in this chapter. In contrast, the structure of caffeine has an additional methyl group at the nitrogen-7 position, decreasing its bronchodilator effect in relation to theophylline. Enprofylline,

TABLE 8.2 Differences in Intensity of Effects for Caffeine and Theophylline

Effect	Caffeine	Theophylline
Central nervous system stimulation	+++	++
Cardiac stimulation	+	+++
Smooth muscle relaxation	+	+++
Skeletal muscle stimulation	+++	++
Diuresis	+	+++

which is not clinically available in the United States at this time, has potent bronchodilating effects, probably because of the large substitution at the nitrogen-3 position.

KEY POINT

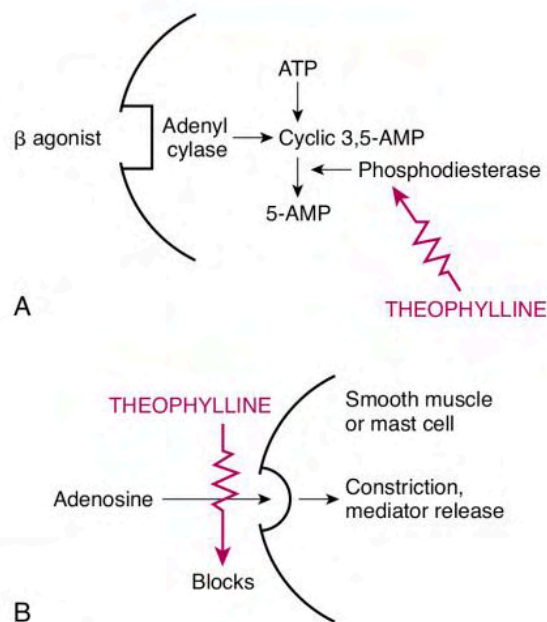
The exact *mechanism of action* of xanthines is unclear; antagonism of adenosine receptors, inhibition of phosphodiesterase, and release of catecholamine.

Proposed Theories of Activity

The exact mechanism of action of xanthines, and theophylline in particular, is unknown.⁸ It was originally thought that xanthines caused smooth muscle relaxation by inhibition of **phosphodiesterase (PDE)**, leading to an increase in intracellular cyclic adenosine 3',5'-monophosphate (cAMP). An increase in cAMP causes relaxation of bronchial smooth muscle. The effect of increased cAMP is described in Chapter 6 in the discussion on β -adrenergic agents. Use of this explanation to account for therapeutic xanthine actions has been questioned, however. Several alternative theories concerning the action of xanthines have been proposed in addition to PDE inhibition. Each of the proposed theories of activity for xanthines is briefly described and discussed in the following sections.

Inhibition of Phosphodiesterase

Theophylline is a weak and nonselective inhibitor of cAMP-specific PDE. The pathway by which this inhibition can lead to an increase in intracellular cAMP, with consequent bronchial relaxation or antiinflammatory effects, is illustrated in Fig. 8.2, A. However, at the dosage levels used clinically in humans, theophylline is a poor inhibitor of the enzyme.⁹ As a result, this may not be the best theory on how xanthines exert a therapeutic effect. PDE is a generic term referring to at least 11 distinct families that have been identified as hydrolyzing cAMP or cyclic guanosine 3',5'-monophosphate (cGMP) and that have unique tissue and subcellular distributions. The various PDE families differ in substrate specificity, inhibitor sensitivity, and cofactor requirements.⁸ There are two cAMP-hydrolyzing PDEs, referred to as PDE3 and PDE4, both of which may play a role in asthma. PDE3 is expressed in regulating heart muscle, vascular smooth muscle, and platelet aggregation. PDE3 inhibitors have been developed to treat heart failure and cardiogenic shock. PDE4 is expressed in airway smooth muscle, pulmonary nerves, and many proinflammatory and immune cells. PDE4 inhibitors suppress processes thought to contribute to asthma inflammation by blocking the degradation of cAMP in target cells and tissue. The antiinflammatory effect of



• **Fig. 8.2** Two proposed mechanisms of action by which theophylline and xanthines reverse airway obstruction. **A**, Inhibition of phosphodiesterase. **B**, Blockade of adenosine receptors. AMP, Adenosine monophosphate; ATP, adenosine triphosphate.

theophylline and xanthines is reviewed in the discussion on the clinical application of these drugs in COPD and asthma.

Antagonism of Adenosine

An alternative explanation of bronchodilation is that theophylline acts by blocking the action of adenosine. This mechanism is illustrated in Fig. 8.2, B. Adenosine is a purine nucleoside that can stimulate α_1 and α_2 receptors. α_1 -receptor stimulation inhibits cAMP, whereas α_2 -receptor stimulation increases cAMP. Inhaled adenosine has produced bronchoconstriction in patients with asthma. Theophylline is a potent inhibitor of both α_1 and α_2 receptors and could block smooth muscle contraction mediated by α_1 receptors.

This explanation is contradicted by the action of enprofylline, which is about five times more potent than theophylline for relaxing smooth muscle yet lacks a sufficient attachment at the nitrogen-1 position to provide adenosine antagonism.¹⁰ This can be seen in Fig. 8.1 by comparing the structures of theophylline and enprofylline. In addition, α_1 receptors are sparse in smooth muscle, and isolated animal tissue preparations have shown smooth muscle relaxation through adenosine stimulation of the α_2 receptors.

Catecholamine Release

A third explanation of xanthine action is that these agents cause the production and release of endogenous catecholamines, which could cause muscle tremor, tachycardia, and bronchial relaxation. Studies on plasma levels of catecholamines, such as epinephrine, have reported conflicting results, with both an increase and no change reported.¹¹

Titrating Theophylline Doses

In the past, clinical use of the xanthine theophylline, in its many forms, was questioned because of wide variability in its therapeutic effect. It was subsequently found that individuals metabolize

theophylline at differing rates, which makes it difficult to determine therapeutic doses. This situation is complicated further by the fact that different forms of the drug are not always equivalent.

Serum Levels of Theophylline

In 1972, Jenne et al.¹² indicated that the optimal serum theophylline level for maximal bronchodilation in adults was 10 to 20 mcg/mL. The effects associated with a range of serum levels are as follows:

- *No effects seen:* Less than 5 mcg/mL
- *Therapeutic range:* 10 to 20 mcg/mL
- *Nausea:* Greater than 20 mcg/mL
- *Cardiac arrhythmias:* Greater than 30 mcg/mL
- *Seizures:* 40 to 45 mcg/mL

CLINICAL CONNECTION

Because individuals vary in the rate at which theophylline is metabolized, dosage must be titrated to clinical effectiveness, avoidance of side effects, and, most precisely, a therapeutic serum level of 5 to 10 mcg/mL in the management of chronic obstructive pulmonary disease (COPD) and 5 to 15 mcg/mL in asthma management. Overall, 10 to 20 mcg/mL is a normal therapeutic range.

Since the originally proposed serum levels of 10 to 20 mcg/mL, the recommended range has been changed to a more conservative 5 to 15 mcg/mL for the management of asthma.¹³ GOLD recommendations for the use of theophylline in COPD suggest a target serum level of 5 to 10 mcg/mL.³ Both these ranges seek maximal therapeutic effect with minimal toxicity and side effects. It is stressed that the ranges listed for toxic effects are general. It is possible for an individual to bypass the nauseous phase of toxicity and immediately enter the seizure phase.

Although there is a dose-related response to higher serum levels of theophylline, there is evidence that the response does not continue at the same rate of increase as levels increase. The improvement in forced expiratory volume in 1 second (FEV₁) tends to flatten above a serum level of 10 to 12 mcg/mL, whereas the toxic effects of theophylline (discussed later in the chapter) tend to increase even within the therapeutic range of 10 to 20 mcg/mL.¹⁴

Dosage Schedules

Because of the variability in the rate at which individuals metabolize theophylline and the other factors that affect theophylline metabolism and clearance rates, dosage schedules are used to titrate the drug. These schedules are found in the product literature, references, such as *Drug Facts and Comparisons* and *Physicians' Desk Reference*, and general pharmacology texts.

For rapid theophyllinization, the patient may be given an oral loading dose of 5 mg/kg, *provided* that the patient was not previously receiving theophylline. This dose is based on anhydrous theophylline. Ideal body weight should be used in calculating theophylline doses because theophylline does not distribute into fatty tissue. In titrating the dose, each 0.5-mg/kg dose of theophylline given as a loading dose results in a serum level of approximately 1 mcg/mL. If theophylline was taken previously by the patient, serum theophylline level should be measured, if possible.

For long-term therapy, a slow titration is helpful, with an initial dose of 16 mg/kg/24 hr or 400 mg/24 hr, whichever is less. These dosages may need to be modified in the presence of such factors

as age (younger children versus older adults), congestive heart disease, or liver disease. The effects of these factors on serum theophylline levels and on dosage are discussed subsequently. The dosage guidelines given have been obtained from theophylline product information.

Dosage of theophylline can be guided by the clinical reaction of the patient or, better, by measurement of serum drug levels. Without serum drug level, the dose of theophylline should be based on the benefit provided and should be reduced if the patient experiences toxic side effects. When monitoring serum theophylline levels, the sample should be taken at the time of peak absorption of the drug—1 to 2 hours after administration for immediate-release forms and 5 to 9 hours after the morning dose for sustained-release forms.

The previous examples of dosage schedules are not complete for all situations; they are intended only as an example of such schedules and of the complexity involved in treating patients with theophylline. Complete tables for different ages and clinical applications should be consulted when administering theophylline.

Theophylline Toxicity and Side Effects

KEY POINT

Theophylline has a *narrow therapeutic margin*, and side effects, such as gastric upset, headache, insomnia, nervousness, palpitations, and diuresis, occur frequently, even within the therapeutic range of dosing. Blood levels of theophylline are affected by many factors, which can either increase or decrease the amount of drug in the body.

An important problem with the use of theophylline is its narrow therapeutic margin; there is very little difference between the dose and serum level that give therapeutic benefit and that cause toxic side effects. Even within the therapeutic serum levels of 10 to 20 mcg/mL, distressing side effects can be experienced. Inhaled theophylline is being studied to research possible reduced side effects.¹⁵ The most common adverse reactions usually seen with theophylline are listed in [Box 8.1](#).

Gastric upset, headache, anxiety, and nervousness are not unusual as less toxic side effects of theophylline and can result in loss of school time or workdays. The diuretic effect should be noted in patients with excess airway secretions (e.g., patients with bronchitis or cystic fibrosis), with adequate fluid replacement when necessary to prevent dehydration and thickening of secretions.

Reactions to levels of theophylline can also be unpredictable in individual patients. Some studies have reported serum levels of 78.5 and 104.8 mcg/mL caused only gastrointestinal symptoms, whereas mean levels of 35 mcg/mL caused cardiac arrhythmias or seizures.¹⁴ Also, minor side effects may provide little warning before serious toxic effects, such as arrhythmias or seizures, occur.

Factors Affecting Theophylline Activity

Theophylline is metabolized in the liver and eliminated by the kidneys. Any condition that affects these organs can affect theophylline levels in the body. Interactions between other drugs and theophylline can affect serum levels of the drug. Some common drugs and conditions that increase or decrease theophylline levels are listed in [Box 8.2](#).

Viral hepatitis or left ventricular failure can cause elevated serum levels of theophylline for a given dose because of decreased

• BOX 8.1 Adverse Reactions Seen With Theophylline Treatment, Organized by Organ System*

Central Nervous System

- Headache
- Anxiety
- Restlessness
- Insomnia
- Tremor
- Convulsions

Gastrointestinal System

- Nausea
- Vomiting
- Anorexia
- Abdominal pain
- Diarrhea
- Hematemesis
- Gastroesophageal reflux

Respiratory System

- Tachypnea

Cardiovascular System

- Palpitations
- Supraventricular tachycardia
- Ventricular arrhythmias
- Hypotension

Renal System

- Diuresis

*Effects are not listed in order of severity or progression.

• BOX 8.2 Factors That Can Increase or Decrease Blood Levels of Theophylline and Affect Dosage Requirements

Increase

- Alcohol (0.9 g/kg)
- β -Blocking agents
- Calcium channel blockers
- Cimetidine, ranitidine
- Corticosteroids
- Disulfiram
- Influenza virus vaccine
- Interferon
- Ephedrine
- Estrogen
- Macrolide antibiotics (e.g., clarithromycin)
- Mexiletine
- Methotrexate
- Pentoxifylline
- Quinolones, oral contraceptives
- Tacrine
- Ticlopidine
- Troleandomycin
- Zileuton

- Cirrhosis
- Congestive heart failure
- Hepatitis
- Pneumonia
- Renal failure

Decrease

- β Agonists
- Aminoglutethimide
- Barbiturates
- Carbamazepine
- Cigarette smoking
- Isoniazid (+ or –)*
- Isoproterenol (IV)
- Ketoconazole
- Loop diuretics (+ or –)*
- Moricizine
- Phenytoin
- Rifampin
- Sulfipyrazone

*+, Increase in theophylline level; –, decrease in theophylline level.

IV, Intravenous.

Data from Weinberger, M., Hendeles, L. (1995). Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *American Journal of Respiratory and Critical Care Medicine*, 152, S77.

liver metabolism of the drug. An opposite effect—decreased serum levels—is caused by cigarette smoking, which stimulates the production of liver enzymes that inactivate methylxanthines¹⁶; this necessitates higher theophylline doses. Some drugs used for the treatment of tuberculosis, such as isoniazid, and the loop diuretics, such as furosemide (Lasix) or bumetanide (Bumex), are unpredictable in their effect and may either increase or decrease theophylline levels. Measurement of serum levels is extremely important when using these agents with theophylline.

β agonists and theophylline have an additive effect and are often combined when treating patients with asthma or COPD. Theophylline may antagonize the sedative effect of benzodiazepines (e.g., Valium). Theophylline can also reverse the paralyzing effect of nondepolarizing neuromuscular blocking agents (pancuronium and atracurium) in a dose-dependent manner. This is important to realize when paralyzing patients with severe asthma to facilitate ventilatory support and when intravenous administration of aminophylline is used.

Clinical Uses of Theophylline

No guidelines for the pharmacologic management of asthma and COPD recommend theophylline as first-line therapy.^{1–3} The disadvantages of theophylline are its narrow therapeutic margin, toxic effects, unpredictable blood levels and need for individual dosing, and numerous drug–drug and drug–condition interactions. The use of theophylline in asthma and COPD is described in the following sections.

CLINICAL CONNECTION

Because of higher risks of side effects and the difficulty in monitoring serum concentration levels, use of theophylline is not recommended in the management of asthma and chronic obstructive pulmonary disease (COPD). Other pharmacologic options with better safety profiles are available.

Use in Asthma

KEY POINT

In the US, theophylline has been relegated to the level of a second- or third-line drug in treating *asthma*. Internationally, GINA recommends against its use in *asthma*.

The role of theophylline preparations in the management of acute and stable asthma and COPD has been debated.^{17,18} In the treatment of asthma, theophylline is suggested for use after reliever agents, such as a β_2 agonist, other controller agents, such as ICS, or mediator antagonists (cromolyn-like drugs) targeting the underlying inflammation or not recommended at all.^{1–3}

Adachi et al.¹⁹ compared a combination of salmeterol and fluticasone propionate with a combination of fluticasone and sustained-release theophylline. Results favored the salmeterol/fluticasone combination in the treatment of patients with moderate asthma. Additionally, the use of intravenous aminophylline in the emergency department did not produce additional bronchodilation or reduce hospital admission compared with standard treatment with β agonists.²⁰

Use in Chronic Obstructive Pulmonary Disease

KEY POINT

In chronic obstructive pulmonary disease (COPD), the *nonbronchodilating effects* of theophylline, such as ventilatory drive stimulation, and enhanced

respiratory muscle function are of value, although the use of theophylline in COPD is still being debated.

Use as a maintenance agent in COPD is indicated if anticholinergics and β_2 agonists fail to provide adequate control. Development of long-acting β_2 agonists, such as salmeterol, formoterol, arformoterol, and olodaterol, offers an additional drug choice to preserve lung function in COPD before using theophylline, especially if theophylline was used to prevent nocturnal symptoms. The increased FEV₁ with salmeterol gives more consistent improvement in lung function on a 12-hour basis and maintains a higher baseline of lung function.²¹ Theophylline is listed as bronchoactive agents for managing an acute exacerbation of COPD in the GOLD guidelines; however, use of other bronchodilators is preferred because of the side effects of theophylline.³

CLINICAL CONNECTION

Chronic obstructive pulmonary disease (COPD) guidelines suggest the use of inhaled β agonists (e.g., albuterol) and anticholinergics (e.g., ipratropium) over the use of theophylline because of its side effects.

Because of side effects in the gastrointestinal system, xanthines are contraindicated in subjects with active peptic ulcers or acute gastritis. Suppositories should not be used if the rectum or lower colon is irritated. If stomach upset occurs with theophylline, the drug may be taken with food. Ingestion of large amounts of caffeine from such sources as tea or coffee may precipitate side effects when taking theophylline.

Nonbronchodilating Effects of Theophylline

Although theophylline is classified as a bronchodilator, it has a relatively weak bronchodilating action. The efficacy of theophylline in obstructive lung disease may result from its nonbronchodilating effects on ventilation. This concept of the effectiveness of theophylline is consistent with the finding of significant clinical improvement despite little increase in expiratory flow rates in patients with asthma.²² Mahler et al.²³ documented the effect of theophylline in reducing dyspnea in patients with COPD when there was no reversibility of obstruction and no objective improvement in lung function, gas exchange, or exercise performance capability. The nonbronchodilating effects of theophylline are provided below with a brief commentary.

Respiratory Muscle Strength

Theophylline can increase the force of respiratory muscle contractility, and this effect is thought to inhibit or reverse muscle fatigue and subsequent ventilatory failure. Theophylline can have the same effect on skeletal limb muscle. Aubier et al.²⁴ showed increased diaphragmatic strength and transdiaphragmatic pressure generation by using electromyographic stimuli before and after theophylline administration.

Respiratory Muscle Endurance

Methylxanthines also show evidence of increasing respiratory muscle endurance and strength. Fatigue of the respiratory muscles can be prevented, especially with increased resistance. Xanthines have been shown to increase the time that an external inspiratory load could be sustained.²²

Central Ventilatory Drive

Methylxanthines have also been shown to increase ventilatory drive at the level of the CNS. In particular, theophylline

can increase phrenic nerve activity for a given level of chemical stimulus.²³ This effect on ventilatory drive seems to occur at the level of the midbrain and may involve the neurotransmitter dopamine.

Cardiovascular Effects

Theophylline use may have nonbronchodilating advantages in patients who have COPD as well as cardiac disease or cor pulmonale. Theophylline can increase cardiac output, decrease pulmonary vascular resistance, and improve myocardial muscle perfusion in ischemic regions.²⁵

Antiinflammatory Effects

Theophylline also has some antiinflammatory effects that may explain its efficacy despite the fact that the drug is a relatively weak bronchodilator.^{17,26} Evidence indicates that theophylline can produce some degree of immunomodulation and an antiinflammatory and bronchoprotective effect through inhibition of cAMP-specific PDE enzymes, particularly PDE3 and PDE4, in proinflammatory cells and tissues. Theophylline has been shown to cause the following (see references for detailed antiinflammatory effects of theophylline^{16,26–31}):

- Decreased migration of activated eosinophils into bronchial mucosa with allergen stimuli and reduced eosinophil survival
- Reduced T-cell proliferation and accumulation in atopic asthma with corresponding improvement in pulmonary function
- Inhibition of proinflammatory cytokines, such as interleukin (IL)-1 β , tumor necrosis factor- α , and interferon- γ , and increased production of the antiinflammatory cytokine IL-10
- Attenuation of the late-phase response to histamine in patients with allergic asthma
- Reduced airway responsiveness to stimuli, such as histamine, methacholine, allergens, sulfur dioxide, distilled water, cyanates, and adenosine
- Increased activation of a group of enzymes, histone deacetylase, also known as *lysine deacetylase*, which are used by corticosteroids to reduce inflammatory response

The antiinflammatory and immunomodulating effects of theophylline occur at lower plasma concentrations (e.g., 9 to 10 mcg/mL) in contrast to the concentrations usually recommended for bronchodilation, and may result in a steroid-sparing effect.²⁷ Inhibitors of PDE4, with more selectivity compared with theophylline and reduced toxic effect profiles, may offer a new class of antiinflammatory agents.⁸ Cosio et al.²⁸ found that the use of low-dose theophylline did not enhance the inflammatory effects of inhaled fluticasone/salmeterol. Additionally, those treated in the study did not experience a reduction in exacerbation when theophylline was added.²⁸

Use in Apnea of Prematurity

When nonpharmacologic methods are unsuccessful in apnea of prematurity, xanthines, such as theophylline and caffeine, are still considered a first-line choice of drug therapy, as stated in the indications for this class of drug. Theophylline is biotransformed to caffeine in neonates.³² However, caffeine is preferable to theophylline for various pharmacologic reasons as follows⁷:

- Caffeine penetrates more readily than theophylline into CSF and can be effective in infants with apnea of prematurity refractory to theophylline therapy.
- Caffeine is a more potent stimulant of the CNS and the respiratory system compared with theophylline.

- Dosing regimens are simpler and give more predictable results with caffeine than with theophylline, most likely because of smaller plasma fluctuations with caffeine.
- Caffeine has a wider therapeutic margin with fewer side effects compared with theophylline.

A standard preparation of caffeine, caffeine citrate (Cafcit), is available, and it can be administered either orally or intravenously. The recommended loading dose is 20 mg/kg of caffeine citrate (equivalent to 10 mg/kg of caffeine); this is followed 24 to 48 hours later by a single daily maintenance dose of 5 mg/kg of caffeine citrate (2.5 mg/kg of caffeine).

RESPIRATORY CARE ASSESSMENT OF XANTHINES

Before Treatment

- Assess the effectiveness of drug therapy on the basis of indications for the aerosol agent: Presence of reversible airflow resulting from primary bronchospasm or obstruction secondary to an inflammatory response or secretions, either acute or chronic.
- Monitor flow rates with bedside peak flow meters, by portable spirometry, or on the basis of laboratory reports of pulmonary function before and after bronchodilator studies, to assess reversibility of airflow obstruction.
- Perform respiratory assessment: Breathing rate and pattern and breath sounds by auscultation, before and after treatment.
- Assess serum blood levels of agent.

During Treatment and Short Term

- Assess the patient's subjective reaction to treatment for any change in breathing effort or pattern.
- Assess arterial blood gases or pulse oximeter saturation as needed for acute states with asthma or COPD to monitor changes in ventilation and gas exchange (oxygenation).

Long Term

- Monitor pulmonary function studies of lung volumes, capacities, and flows.
- Instruct asthmatic patients in the use and interpretation of disposable peak flow meters to assess the severity of asthmatic episodes and to ensure there is an action plan for treatment modification.
- Patient education should emphasize that xanthines do not treat underlying inflammation or prevent progression of asthma or COPD, and additional antiinflammatory treatment or more aggressive medical therapy may be needed if there is a poor response to the agent.
- Because the agent is systemic, assess ongoing function of all body systems.
- Assess serum blood levels of agent.

General Contraindications

- Xanthines have a narrow therapeutic index margin. Overdosing is possible and should be monitored.
- Because of different body systems being affected, all patients should be closely monitored.
- Patients with chronic disease (cystic fibrosis, COPD, and asthma) may consider using other agents with better safety profiles, such as corticosteroids.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What drug in the xanthine group is used most often therapeutically?
2. In what formulations is theophylline available?
3. What is the recommended therapeutic plasma level for theophylline in asthma and COPD?
4. How do you know whether a given dose of theophylline would produce a satisfactory treatment effect in a patient with asthma?
5. Identify at least three adverse side effects seen with theophylline.
6. What is meant by a “narrow therapeutic margin”?
7. Although theophylline is a weak bronchodilator, what other effects make it useful in treating chronic airflow obstruction?
8. True or False: Theophylline causes bronchodilation and improved airflow solely by inhibiting PDE, which breaks down cAMP.

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 70-year-old White man arrived at the emergency department. He was severely short of breath and could take only a few steps before complaining of dyspnea. He reported coughing up thick, greenish sputum with some tinges of blood in the last few days. He appeared oriented, coherent, and malnourished, with thin arms. On interview, he admitted to smoking two packs of cigarettes a day since age 18 years but stopping smoking about 2 years ago. He has had six hospitalizations within the last 2 years. Current medications include ipratropium bromide via a metered dose inhaler (MDI), 2 puffs four times daily, with a β_2 agonist, as needed, 1 to 3 puffs. He has been using the β_2 -agonist MDI regularly during the last month, at least four times daily.

On physical examination, he was very short of breath, even at rest; he used his accessory muscles and had a respiratory rate (RR) of 22 breaths/min. There was little discernible chest expansion. His breath sounds were distant in all areas, with expiratory wheezes, and air movement appeared poor. He was afebrile, pulse (P) was 120 beats/min, and blood pressure (BP) was 170/112 mm Hg.

Laboratory values on admission showed normal electrolyte levels, but his white blood cell count (WBC) was $15.2 \times 10^9/\text{mL}$, and his hemoglobin was 10.6 g/dL. Arterial blood gas values on room air were as follows: pH 7.40, arterial carbon dioxide pressure (PaCO_2) 42.4 mm Hg, arterial oxygen pressure (PaO_2) 64 mm Hg, base excess +1.9 mEq/L, and arterial oxygen saturation (SaO_2) 90%.

A posteroanterior chest radiograph shows hyperinflation of the lung fields, with flattened diaphragms.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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9

Mucus-Controlling Drug Therapy

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CHAPTER OUTLINE

Drug Control of Mucus: A Perspective

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Submucosal Mucous Glands

Ciliary System

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Maneuver

Autogenic Drainage

Exercise

Positive Airway Pressure

High-Frequency Chest Wall Compression

Oscillatory Positive Expiratory Pressure

Chest Wall Compression

Future Mucus-Controlling Agents

Respiratory Care Assessment of Mucoactive Drug Therapy

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to mucus-controlling drug therapy
2. Interpret the physiology and mechanisms of mucus secretion and clearance
3. Name the types of mucoactive medications and their presumed modes of action
4. Describe the medications approved for the therapy of mucus clearance disorders and their approved indications
5. Identify the contraindications to the use of mucoactive medications
6. Explain the interaction between airway clearance devices or physical therapy and mucoactive medications

KEY TERMS AND DEFINITIONS

Adhesives Substances that reduce adhesion.

Elasticity Rheologic property characteristic of solids; it is represented by the storage modulus G' (energy storage).

Expectorants Medications meant to increase the volume or hydration of airway secretions.

Gel Macromolecular description of pseudoplastic material having both viscosity and elasticity.

Glycoproteins Proteins with attached oligosaccharide (sugar) units.

Mucins The principal solid constituents of normal mucus. High-molecular-weight glycoproteins that give mucus its physical properties, such as viscoelasticity.

Mucoactive agent Term connoting any medication or drug that has an effect on mucus secretion; may include mucolytic, expectorant, mucospissic, mucoregulatory, or mucokinetic agents.

Mucokinetic agents Medications that increase cough or ciliary clearance of respiratory secretions.

Mucolytic agent Medications that degrade polymers in secretions. Classic mucolytics degrade mucin, and peptide mucolytics break pathologic filaments of DNA or actin in sputum.

Mucoregulatory agents Drugs that reduce the volume of airway mucus secretion and appear to be especially effective in hypersecretory states, such as bronchorrhea, diffuse panbronchiolitis (DPB), and some forms of asthma (see *secretory hyperresponsiveness*).

Mucospissic agents Medications that increase viscosity of secretions and may be effective in the therapy of bronchorrhea.

Mucus Secretion from surface goblet cells and submucosal glands composed of water, proteins, and glycosylated mucins. The glycoprotein portion of the secretion is termed mucin. Mucus (noun) is the secretion; mucous (adjective) is the cell or gland type.

Oligosaccharide Sugar that is the individual carbohydrate unit of glycoproteins.

Phlegm Purulent material in the airways. From the Greek word for inflammation. When expectorated, phlegm is called sputum.

Rheology Study of the deformation and flow of matter in response to an applied stress.

Secretory hyperresponsiveness Mucus hypersecretion in response to airway infection, cancer, or inflammation. Some forms of asthma are characterized by bronchospasm, or bronchial muscle hyperresponsiveness, while other have more of a hypersecretory response.

Sol Also called the periciliary layer; it is the weak gel containing attached mucins that bathes the beating cilia and usually separates that mucus layer from the epithelial surface.

Sputum Expecterated phlegm that contains respiratory tract, oropharyngeal, and nasopharyngeal secretions, bacteria, and products of inflammation, including polymeric DNA and actin.

Viscosity Resistance of liquid to sheer forces or energy loss with applied stress; a rheologic property characteristic of liquids and represented by the loss modulus G'' .

Chapter 9 presents an in-depth review of the mucociliary system and the nature of mucus as a basis for discussing pharmacologic agents used in the treatment of respiratory secretions. The drugs currently used in North America by aerosol administration—*N*-acetyl cysteine (NAC; Mucomyst), dornase alfa (Pulmozyme), and hyperosmolar saline (Hypersal)—are discussed, along with investigational agents, and future directions for mucoactive drug therapy are outlined.

Drug Control of Mucus: A Perspective

KEY POINT

Mucoactive therapy should be considered after therapy to decrease infection and inflammation.

The self-renewing, self-cleansing mucociliary escalator is a major defense mechanism of the lung. Failure of this system results in mechanical obstruction of the airway, often with thickened, adhesive secretions. A slowing of mucus transport is reported in many diseases associated with abnormal mucociliary function.^{1,2} Whether such slowing is due to changes in the physical properties of mucus, decreased ciliary activity, or both is not always clear. Mucus is found in many areas of the body exposed to the outside environment, including the airways, gastrointestinal tract, eyes, and genitourinary tract. Regardless of its location, mucus is protective, lubricating, and waterproofing, and it protects against osmotic or inflammatory changes. The mucus barrier can also entrap microorganisms, inhibiting chronic bacterial infection and biofilm formation.

Historically in respiratory care, drug therapy for secretions has been aimed at liquefying thick mucus to a watery state (called *mucolysis*). Because mucus is a **gel** with physical properties of

viscosity and elasticity, drug therapy for mucus clearance disorders should affect the physical properties of the mucus gel to improve cough or mucociliary clearance. Thinning of secretions, or mucolysis, can decrease secretion clearance, thus the term **mucolytic agent** is better replaced with **mucoactive agent**. A review of mucus physiology presents the concepts necessary for discussing the current and possible future pharmacologic management of retained secretions.

Clinical Indication for Use

CLINICAL CONNECTION

Mucus lubricates, waterproofs, and protects against osmotic or inflammatory changes. The normal mucus barrier can entrap microorganisms, inhibiting chronic bacterial infection and biofilm formation.

The general indication for mucoactive therapy is to reduce the accumulation of airway secretions, improving pulmonary function and gas exchange and preventing repeated infection and airway damage. Diseases in which mucoactive therapy is indicated are those with hypersecretion or poor clearance of airway secretions, including chronic bronchitis (CB), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), asthma, and bronchiectasis. Not all patients with mucus retention benefit from mucoactive drug therapy; those who have strong expiratory airflow and cough usually have a better response. The use of mucoactive therapy to promote secretion clearance should be considered after therapy to decrease infection and inflammation and after minimizing or removing irritants to the airway, including tobacco smoke.³

Classification of Mucoactive Medications

Table 9.1 presents general information about mucoactive agents that are approved, available, or commonly administered as inhaled aerosols in the United States. Greater detail is given on indications, dosage and administration, hazards and side effects, and assessment of drug therapy in discussions of individual agents.⁴

Mucoactive medications differ in their mechanisms of action. Secretion properties that impair airway clearance also differ

among different diseases and at different times in the course of a disease. The source and properties of airway secretions and the mechanisms of action for the mucoactive agents are the basis for clinical use of these drugs.

Physiology of the Mucociliary System

Source of Airway Secretions

The conducting airways in the lung and the nasal cavity to the oropharynx are lined by a mucociliary system, illustrated diagrammatically in Fig. 9.1. The secretion lining the surface of the airway is called **mucus** and has been described as having two phases: (1) A gel layer (0.5 to 20 μm) is propelled toward the larynx by the cilia and lies atop (2) a weak gel periciliary layer about the height of a fully extended cilium.³ Cells responsible for secretion in the airway and the source of components found in respiratory mucus have been summarized by Voynow and Rubin.⁵ Although there are many cell types in the mammalian airway, the essential secretory structures of the mucociliary system are the following:

- Surface epithelial cells
 - Pseudostratified, columnar, ciliated epithelial cells
 - Surface goblet (or mucous) cells
 - Club cells (formerly called Clara cells) in the distal airway
 - Submucosal glands, with serous and mucous cells
- Submucosal glands are found in cartilaginous airways. These mucus-producing glands are not found beyond the distal airways. Mucus secreted by surface epithelial cells and glands in the airway provides for basic protection of the respiratory tract, including humidification and warming of inspired gas, mucociliary transport of debris, waterproofing and insulation, and antibacterial activity.³

Terminology: Mucus, Phlegm, and Sputum

There has been confusion regarding the nomenclature used to classify mucoactive medications. Although some have used “mucolytic” as a generic term, most of these medications are thought to mobilize secretions by mechanisms other than by the direct “thinning” of mucus. For example, although the mucociliary transportability of sputum may be improved by reducing sputum viscosity

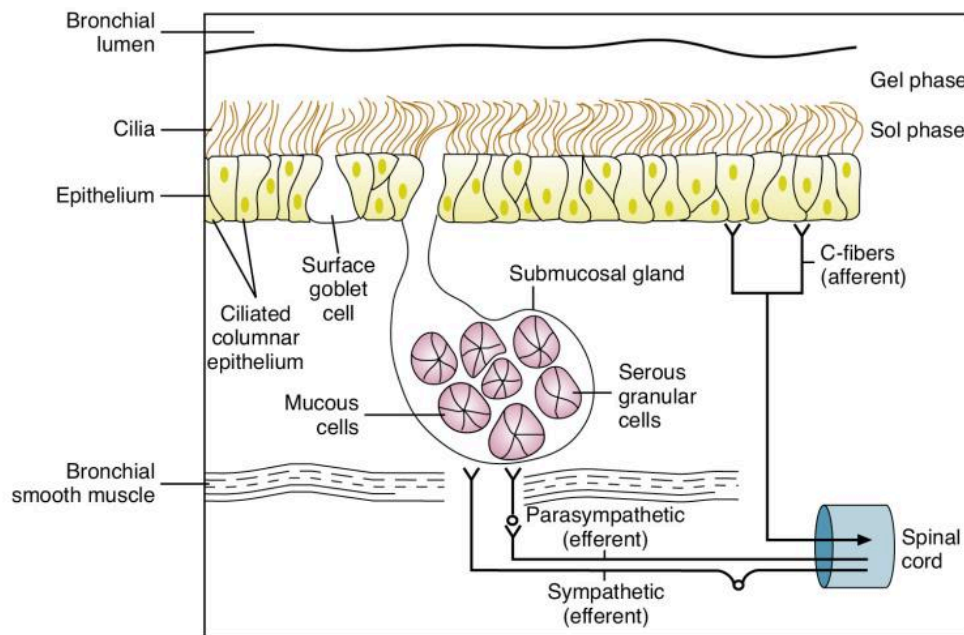
TABLE 9.1 Mucoactive Agents Available for Aerosol Administration

Drug	Brand Name	Adult Dosage	Use
<i>N</i> -Acetylcysteine L-cysteine (NAC)	10% Mucomyst, 20% Mucomyst	SVN: 3–5 mL	Efficacy has not been demonstrated with any dose of NAC for any lung disease
Dornase alfa	Pulmozyme	SVN: 2.5 mg/ampule, one ampule daily*	Cystic fibrosis (CF) only
Aqueous water, saline	—	SVN: 3–5 mL, as ordered	Sputum induction
Hyperosmolar 7% saline	Hyper-Sal PulmoSal	SVN: 4 mL	Airway clearance (mucokinetics) for therapy of CF (7% saline and Mannitol)
Dry powder mannitol 3% hyperosmolar saline	Bronchitol Aridol†		3% saline used for infantile bronchiolitis

*Use recommended nebulizer system—see package insert.

†Approved in the United States for bronchial challenge testing.

SVN, Small volume nebulizer.



• **Fig. 9.1** Principal components and innervation of the mucociliary system in the respiratory tract.

while preserving elasticity, the ability to clear secretions via cough is greater with *increased* sputum viscosity and decreased adhesivity. Knowledge of mucus properties has given us tools to better understand the mechanisms of airway disease and mucoactive therapy. The currently accepted terminology is defined in the *Key Terms and Definitions* list at the start of this chapter. For more details on current terminology and its evolution, see Reid and Clamp,⁶ Basbaum,⁷ Voynow and Rubin,⁵ and King and Rubin.⁸

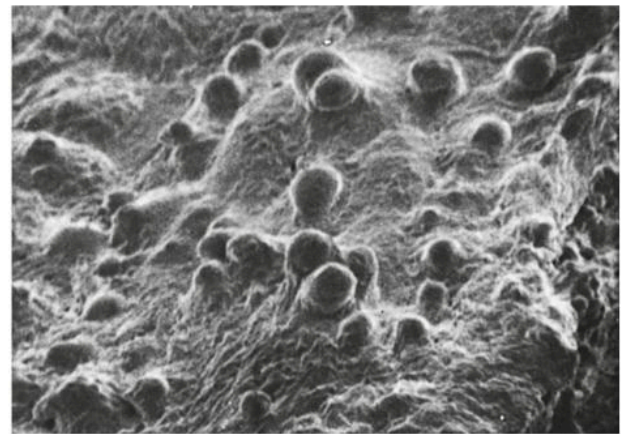
Surface Epithelial Cells

The surface of the healthy trachea and bronchi primarily includes ciliated and goblet cells, at a ratio of approximately 5: 1. There are more than 6000 goblet cells per square millimeter of normal airway mucosa. Goblet cells do not seem to be directly innervated in the human lung, although they respond to irritants and inflammatory mediators and peptides by increasing the production of mucus and are, themselves, immune effector cells that respond to diverse signaling peptides, including those secreted by ciliated cells. Figs. 9.2 and 9.3 show scanning electron micrographs of the mucus lining⁹ (Fig. 9.2) and of the bronchiolar surface with the mucus stripped away⁹ (Fig. 9.3). In addition to ciliated and goblet cells, microvilli, which may have absorptive and sensory functions, can be seen in Fig. 9.3.

Submucosal Mucous Glands

Submucosal glands below the epithelial surface are thought to provide much of the mucin on the airway surface. The submucosal gland is under parasympathetic (vagal) control and responds to cholinergic stimulation by increasing the amount of mucus secreted. Evidence also suggests that submucosal glands in the respiratory tract are innervated by sympathetic axons and the peptidergic nerve system.

Two types of cells, mucous and serous, are found in the glands. Fig. 9.4 shows a section of ferret airway stained for mucin, with the surface mucous (goblet) cells and the submucosal gland's



• **Fig. 9.2** Scanning electron micrograph of the mucus blanket in a bronchiole, prepared from hamster lung. (From Nowell JA, Tyler WS. [1971]. Scanning electron microscopy of the surface morphology of mammalian lungs. *The American Review of Respiratory Disease*, 103[3], 313–328.)

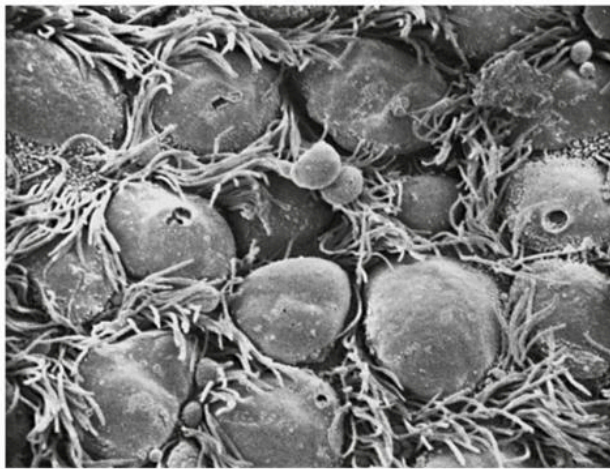
serous and mucous cells identified. Secretions from the serous and mucous cells mix while exiting the submucosal gland and are transported through a ciliated duct onto the airway lumen.

Ciliary System

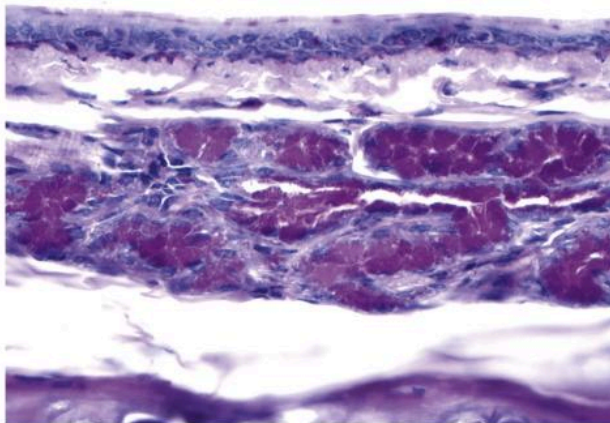
KEY POINT

The airway secretion consists of a *mucus layer*, where *mu*cin glycoprotein is secreted, and a weak gel *periciliary layer*.

Droplets of mucus from the secretory cells form plaques in the distal, nonciliated airway, and these coalesce into a continuous layer in the more proximal ciliated airway. Mucociliary transport results from the movement of the mucus gel by the beating cilia. There are approximately 200 cilia on each ciliated cell. Cilia are about 7 μ m in length in larger airways and shorten to 5 μ m or less



• **Fig. 9.3** Scanning electron micrograph of the airway surface shows epithelial cells with cilia, possible surface goblet cells dehiscing, and some microvilli. (From Nowell JA, Tyler WS. [1971]. Scanning electron microscopy of the surface morphology of mammalian lungs. *The American Review of Respiratory Disease*, 103[3], 313–328.)



• **Fig. 9.4** Light microscopy showing immunohistochemical staining of ferret airway, using horseradish peroxidase-conjugated *Dolichos biflorus* agglutinin. Tracheal section shows the mucociliary apparatus, including surface mucous (goblet) cells, ciliated epithelial cells, and serous and mucous glands.

in smaller bronchioles. Luk and Dulfano¹⁰ examined the ciliary beat frequency on biopsy samples from various tracheobronchial regions and found rates of 8 to 18 Hertz (Hz) (Hz = 1 cycle/sec) at 37° C. A ciliary beat is composed of an *effective* (power) stroke and a *recovery* stroke with about a 1: 2 ratio. In the effective stroke, the cilium moves in an upright position through a full forward arc to contact the underside of the mucus layer and propel it forward. In the recovery stroke, the cilium swings back around to the starting point near the cell surface to avoid pulling secretions back. Cilia beat in a coordinated or metachronal wave of motion to propel airway secretions.¹¹ A functional surfactant layer lies at the tips of the cilia and separates the periciliary fluid from the mucus gel. This layer allows the cilia to transmit kinetic energy effectively to the mucus without becoming entangled. This layer also facilitates mucus spreading as a continuous layer and prevents water loss from the periciliary fluid.

TABLE 9.2 Effects of Various Drug Groups on Mucociliary Clearance

Drug Group	Ciliary Beat	Mucus Production	Transport
β-Adrenergic agents	Increase	Increase*	±
Cholinergic agents	Increase	Increase†	Increase
Methylxanthines	Increase	Increase†	±
Corticosteroids	None	None†	None
Anticholinergics	None	Decrease in some circumstances	None

*Data from Wanner, A. (1977). Clinical aspects of mucociliary transport. *American Review of Respiratory Disease*, 116(1), 73–125.

†Data from Iravani, J., & Melville, G. N. (1975). Mucociliary activity in the respiratory tract as influenced by prostaglandin E. *Respiration*, 32, 305.

Factors Affecting Mucociliary Transport

Mucociliary transport velocity varies in the normal lung and has been estimated at about 1.5 mm/min in peripheral airways and 20 mm/min in the trachea. Transport rates are slower in the presence of the following conditions or substances, many of which are associated with airway damage:

- Chronic obstructive pulmonary disease (COPD) and CF
- Airway drying (e.g., with the use of dry gas for mechanical ventilation)
- Narcotics
- Endotracheal suctioning, airway trauma, and tracheostomy
- Tobacco smoke and tobacco smoke extract
- Atmospheric pollutants (SO₂, NO₂, ozone) and allergens may increase transport, especially at low concentration, but at higher, toxic concentrations or with prolonged exposure, these decrease transport rates
- Hyperoxia and hypoxia

Table 9.2 summarizes the effects of drug groups commonly used in respiratory care on ciliary beat, mucus output, and overall transport.

CLINICAL CONNECTION

It is more than acceptable for patients with pulmonary disorders to drink milk. Milk does not increase mucus or congestion in the respiratory system.

Food Intake and Mucus Production

A common belief is that drinking dairy milk increases the production of mucus and congestion in the respiratory tract. Respiratory care personnel may be asked for advice on withholding milk from children with colds, respiratory infections, or chronic respiratory conditions such as CF.¹² In a study of 60 healthy subjects with experimentally induced rhinovirus respiratory infections, milk intake ranged from 0 to 11 glasses a day. There was no association between milk or dairy product intake and respiratory tract symptoms of congestion or nasal secretion weight. None of the subjects were allergic to cow's milk. The investigators concluded that the data do not support the withholding of milk or the belief that milk increases respiratory tract congestion.

Secretory Hyperresponsiveness and Mucus Hypersecretion

The term “**secretory hyperresponsiveness**” is used for increased mucus secretion either intrinsically or in response to bronchoprovocation. Certain groups of patients appear to have greater mucus secretory response, including those with middle lobe syndrome, cough-dominant (“cough-variant”) asthma, and severe asthma. Secretory hyperresponsiveness also is a component of forms of lung cancer associated with bronchorrhea. Secretory hyperresponsiveness and mucus hypersecretion appear to be related to activation of the extracellular regulated kinase (ERK1/2), signaling.

Nature of Mucus Secretion

A healthy person is thought to produce about 100 mL of mucus every 24 hours that is clear, viscoelastic, and sticky. Most of this secretion is reabsorbed in the bronchial mucosa or swallowed with saliva. The individual rarely notices this. During disease, the volume of secretions can increase dramatically and secretion clearance can be decreased so that secretions are expectorated or swallowed. A primary function of respiratory tract mucus is thought to be transporting and removing trapped inhaled particles, cellular debris, and dead cells.

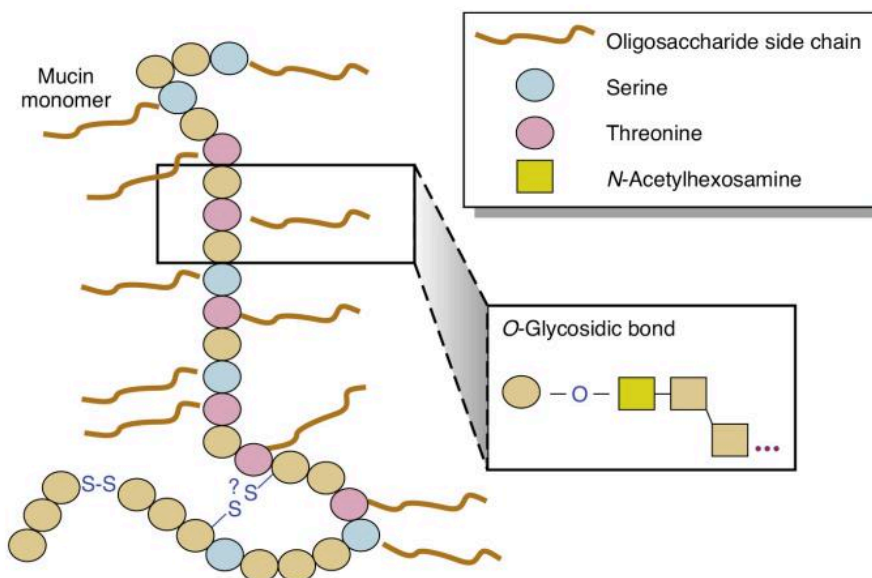
Structure and Composition of Mucus

The structure and major constituents of the mucus secreted by submucosal glands and surface goblet cells are pictured in Fig. 9.5 and have been reviewed elsewhere.^{5,7,13–16} Airway mucus forms a protective barrier between the respiratory tract epithelium and the environment. Mucus is composed mainly of water and ions, with approximately 5% of the content from proteins secreted by airway cells and lipids.^{17–19} In health, the mucin **glycoproteins** are the major macromolecular component of the mucus gel. **Mucins** are responsible for the protective and clearance properties of mucus.^{20–22} Data suggest that the transportability of the mucus layer is dependent on the concentration of mucins in the mucus layer as a function of the mucin concentration to the power of 2.5.²³

There are two major classes of mucins: the secreted and the membrane-tethered mucins.^{24,25} Four secreted mucins (MUC2, MUC5AC, MUC5B, and MUC6) have genes that are clustered on chromosome 11p15 and contain domains with significant homology to the von Willebrand factor D domains that are sites for oligomerization.²⁶ In sputum, MUC5AC and MUC5B are the major oligomeric gel-forming mucins.²⁷ MUC5AC is produced primarily by the goblet cells in the tracheobronchial surface epithelium, whereas MUC5B is secreted primarily by the submucosal glands, although the goblet cell is also capable of secreting MUC5B.²⁸ The membrane-tethered mucins, MUC1, MUC3, MUC4, MUC12, and MUC13, and MUC 16, contain a transmembrane domain and a short cytoplasmic domain.²⁶ At least 12 mucin genes (*MUC1*, *MUC2*, *MUC4*, *MUC5AC*, *MUC5B*, *MUC7*, *MUC8*, *MUC11*, *MUC13*, *MUC15*, *MUC19*, and *MUC20*) have been observed at the mRNA level in tissues of the lower respiratory tract from healthy individuals.^{24,26,29–35}

Mucus is a complex, high-molecular-weight macromolecule consisting of a mucin protein backbone to which carbohydrate (**oligosaccharide**) side chains are attached. The airway mucus gel-forming mucins are primarily MUC5AC and MUC5B; the periciliary layer contains tethered mucins including MUC1 (a signaling mucin also found in some cancers that is able to regulate inflammation), MUC4, and MUC 16.^{23,30,36,37} The carbohydrate content is 80% or more of the total weight of the macromolecule. This structure is similar to a bottlebrush in appearance. This general structure of protein and attached oligosaccharide side chains is termed a *glycoprotein*. Mucin forms a flexible, threadlike strand 200 nm to 6 μ m in length³⁸ that is linearly cross-linked with disulfide bonds bridging adjacent cysteine residues. Strands may also be linked with each other by hydrogen bonding and van der Waals forces. The result is a gel that consists of a high water content (90% to 95%) organized around the structural elements and that is intensely hydrophilic and spongelike.^{39,40}

Under normal circumstances, bonding within mucus produces low viscosity but moderate elasticity. Although mucus incorporates water during its formation, a gel acts like both a liquid and a solid. For example, cooking gelatin is mostly water but organizes into a semisolid by its chemical structure as the liquid gels. It is important clinically that sufficient water must be available to form



• **Fig. 9.5** Basic structure and constituents of the mucus macromolecule. S–S–, Disulfide bonds.

mucus with normal physical properties, but once formed, mucus does not readily incorporate additional water.⁴¹ Phospholipids are also present in the serous cell granules of the submucosal glands. When released onto the airway surface, phospholipids serve as lubricants affecting the surface-active and adhesive properties of mucus, both of which can affect mucociliary transport.³

In addition to the mucus gel secreted in the airway, bronchial secretions contain serum and secreted proteins including cytokines, lipids, and electrolytes. Antibacterial defense in the airway is provided by mucin, secretory immunoglobulin A (IgA), immunoglobulin G (IgG), lysozyme, lactoferrin, defensins, and peroxidase and serine proteases. Bronchial secretions control the potentially destructive action of protease enzymes with two major antiproteases: α_1 -protease inhibitor and secretory leukoprotease inhibitor (sLPI), a cationic protein found in serous secretory glandular cells.³ In healthy airways, antiproteases are present in higher quantities than protease enzymes and provide a protease screen.⁴² These antiproteases also prevent abnormal mucin degradation *in vitro* as reported in CF and in CB.^{43,44}

Mucus protects the mucosal surface by selectively trapping pathogens or foreign particles into its dense polymeric microstructure and clears them by means of mucociliary clearance, while it allows rapid passage of nutrients and antibodies.^{45–47} Mucus is primarily composed of long and heavily glycosylated macromolecules called mucins that link via end-to-end disulfide bonds to form mesh-like structural networks. This is mediated by reversible bonds and stabilized by electrostatic repulsive force between charged sugar side chains.⁴⁸ The strength of the molecular configuration and network rely on the concentration of ions and small macromolecules present within the mucus.⁴⁹ The characteristic mechanical properties of mucus depend on the regulation of various mucus components (mucin, DNA, lipids, proteins, cells, water) and are highly interdependent. Alteration in any of these components can affect the properties of mucus.

The microstructure of native mucus is highly heterogeneous with pore sizes of nanometers to micrometers. In persons with airway disease, the homeostatic balance of ions is impaired along with the changes in airway surface liquid.^{45,50} These alterations can change mucus permeability and microstructure, such as mesh size and viscosity. This can adversely alter neutrophil migration and pathogens capture.^{50–52}

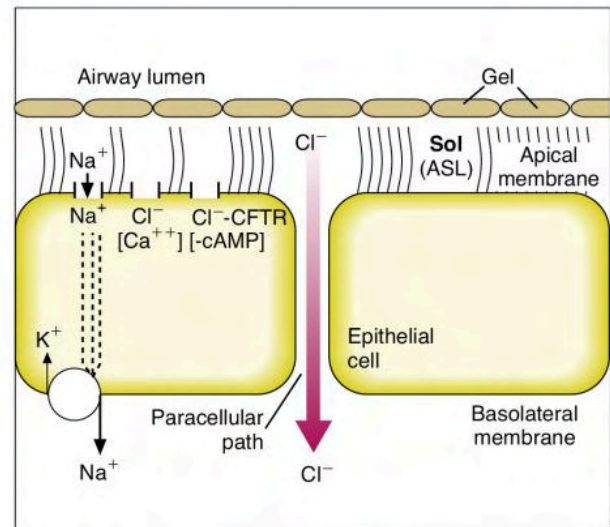
As in CF patients with reduced lung function, the key biochemical components of mucus such as mucin, DNA, and solid content changes, and quantitative analysis of mucus microstructure using particles probes shows a decrease in mucus mesh size.⁵⁰ Therefore, microstructural analysis of airways mucus may serve as a marker of respiratory disease and a potential target for therapy.

Epithelial Ion and Water Transport

KEY POINT

Epithelial ion exchange in the airway surface liquid maintains normal periciliary fluid depth.

The composition and volume of the periciliary fluid layer is regulated in part by ion transport across the epithelial cells lining the airway lumen. If the periciliary layer is not approximately the height of an extended cilium, mucus movement is less effective.⁵³ Defective ion transport may contribute to the cycle of retained secretions and infection seen in CF.^{54,55} Normal airway epithelial ion transport is illustrated in Fig. 9.6.



• **Fig. 9.6** Illustration of ion-exchange mechanisms across normal airway epithelium controlling absorption and secretion for the periciliary airway surface liquid (ASL). Under basal conditions, sodium (Na⁺) is absorbed along with liquid, with no net chloride (Cl⁻) secretion from the cell into the liquid layer. cAMP, Cyclic adenosine 3',5'-monophosphate; CFTR, cystic fibrosis transmembrane ion conductance regulator; K⁺, potassium ion.

In the basal, unstimulated state, sodium (Na⁺) absorption into the epithelial cell is the dominant ion exchange that absorbs liquid from the airway periciliary layer. Na⁺ absorption occurs as an active transport process through Na⁺ channels, the epithelial Na⁺ channel [ENaC], on the apical or airway side of the cell. Na⁺ in the epithelial cell is pumped from the cell, driven by a sodium/potassium-ATPase pump on the basolateral membrane of the epithelial cell, as shown in Fig. 9.6. When Na⁺ is absorbed from the airway surface liquid, there is an accompanying absorption of chloride (Cl⁻) ions and water.⁵⁶ Cl⁻ secretion can occur through at least two different types of Cl⁻ channel in the cell apex. One channel is dependent on cyclic adenosine 3,5'-monophosphate (cAMP), the CF transmembrane ion-conductance regulator (CFTR) channel; the other channel is calcium activated.

To summarize, under normal conditions, healthy airway epithelia can absorb salt and water driven by an active Na⁺ transport. Normal epithelia can also secrete liquid into the periciliary fluid driven by active Cl⁻ transport through ion channels and passively through aquaporins or water channels.

Secretions in Disease States

KEY POINT

Mucus or mucociliary clearance can be abnormal in pulmonary diseases such as chronic bronchitis (CB), asthma, or cystic fibrosis (CF).

The normal clearance of airway mucus can be altered by changes in the volume, hydration, or composition of the secretion, as well as by changes in ciliary function. The composition of respiratory mucus is undergoing investigation based on structural analysis techniques.^{57,58}

Knowledge of these features of respiratory mucus may lead to a better understanding of diseases characterized by an abnormal production of mucus, such as CB and asthma, in which there

is mucus hypersecretion, and CF, in which there is a decrease of intact mucin but an increase of pathologic DNA-actin polymers. Although it had been hypothesized that patients with CF hypersecrete viscous mucus, leading to airway obstruction, it has been shown that tenacious (but not viscous) secretions that characterize CF airway disease are composed almost entirely of DNA—rich with characteristics most similar to pus rather than to normal airway mucus.⁵⁹ Secreted CF mucins are rapidly degraded by serine proteases (including bacterial proteases) in the airway. This also occurs during exacerbations of CB. Airway damage may predispose patients to bacterial infections in CB because of impaired clearance of mucus.

Sputum, or expectorated phlegm, is composed of mucus mixed with inflammatory cells, cellular debris, polymers of DNA and filamentous (F)-actin, and bacteria. Mucus is usually cleared by airflow and ciliary movement, and sputum is cleared by cough.⁶⁰ Purulent, green **phlegm** is caused by the neutrophil-derived enzyme myeloperoxidase, indicating neutrophil activation.⁶¹ Bronchial obstruction by secretions can increase airflow resistance and lead to complete airway obstruction and atelectasis.¹⁴ Regardless of whether the airway is full of mucus or phlegm, effective airway clearance is important for airway hygiene.

Chronic Bronchitis

CB is defined clinically as daily sputum expectoration for 3 months of the year for at least 2 consecutive years, usually in a tobacco smoker or ex-smoker. In the airway of a subject with CB, there is hyperplasia of submucosal glands and goblet cells. The number of goblet cells increases and there is hypertrophy of the submucosal glands, as measured by the Reid Index of gland-to-airway wall thickness ratio.⁶² When studied in vitro, it was found that submucosal glands from subjects with CB produce excessive amounts of mucus.⁶³ Tobacco smoke is considered the most important predisposing factor to airway irritation and mucus hypersecretion, but other factors can include viral infections, pollutants, and genetic predisposition.^{14,64} It has been reported that chronic sputum expectoration is associated with a more rapid decline in lung function and, for persons with COPD, more frequent admissions to the hospital.⁶⁵

Asthma

Mucus hypersecretion can occur during an acute asthmatic episode or can be a chronic feature of asthma, accompanying airway inflammation. It has been reported⁶⁶ that as many as 80% of patients with asthma report increased sputum expectoration.

In acute severe and fatal asthma, there is profound hypersecretion of highly viscous and rigid mucus, leading to complete airway obstruction.⁶⁷ Because most of these patients have received large amounts of β -agonist bronchodilators, sometimes even by the intravenous route, it is likely that β receptors are fully saturated. β Agonists may induce the secretion of viscous mucus and may contribute to airway obstruction.⁶⁸

Bronchorrhea

Bronchorrhea is defined as the production of large volumes of watery sputum. This occurs in about 9% of adults with chronic asthma.⁶⁹ Some of these patients respond well to antiinflammatory therapy such as corticosteroids,⁷⁰ indomethacin by aerosol,⁷¹ anticholinergic medications, or macrolide antibiotics.⁷² These are considered mucoregulatory medications and are most effective when bronchorrhea is associated with airway inflammation. Patients with congenital fucosidosis also have a form of

bronchorrhea caused by the inability of mucins to polymerize. This form of bronchorrhea does not respond to mucoregulatory therapy.⁷³

Plastic Bronchitis

Plastic bronchitis is a rare disease characterized by the formation of large gelatinous or rigid branching airway casts.⁷⁴ This is dramatically different from the mucus or sputum plugs expectorated by patients with purulent airway diseases like CF because the plastic bronchitis casts repeat airway branching. Plastic bronchitis has not been shown to occur as a result of CF, asthma, or bronchiectasis. Casts are often too thick and slippery to be easily suctioned through a bronchoscope and too friable to be grasped and removed with forceps so freezing and cryoprobe extraction is usually performed at bronchoscopy. Some patients are able to expectorate even large casts spontaneously. Not all patients expectorate casts, and this may delay the diagnosis.

The prevalence of plastic bronchitis is unknown. This disease may also overlap with diseases such as asthma and with the severe mucus plugging sometimes seen in bronchopulmonary *aspergillosis* or middle lobe syndrome. Differentiating between severe asthma with mucus plugging and plastic bronchitis can be difficult.

Plastic bronchitis takes two main forms.⁷⁵ Typical or lymphatic plastic bronchitis is the most common form and is associated with abnormalities in pulmonary lymphatic drainage. This most commonly occurs in children with congenital heart disease, usually single ventricle or Fontan physiology, who has anatomic abnormalities of the pulmonary lymphatic drainage and thoracic duct that leads to lymph (chyle) leak into the airway where it congeals into casts. This form of plastic bronchitis can also be seen in persons with congenital lymphatic abnormalities (often genetic), lymphatic cancer, or poor cardiac output as has been reported in patients with sickle cell disease. Although these casts have been described as “fibrinous,” there is little or no fibrin present when stained specifically.

The other form of plastic bronchitis is called eosinophilic plastic bronchitis and the casts, which are more friable than the lymphatic form, contain eosinophils and eosinophil breakdown products like Charcot-Leyden crystals. Despite the large amount of airway eosinophils, few of these patients have a history of asthma, and asthma medications, like bronchodilators, have little effect. This condition more closely resembles eosinophilic esophagitis than asthma. Eosinophilic plastic bronchitis usually occurs in older persons, and many have obesity as a comorbidity. The casting usually follows a respiratory tract infection and often occurs in the same part of the lung each time. This form of plastic bronchitis rarely causes death, and in many cases, casting will completely stop after a variable amount of time.

In patients with lymphatic plastic bronchitis, inhaled heparin, dietary modification, or thoracic duct ligation may help. Aerosol tissue plasminogen activator (tPA) has been shown to help some patients with active cast formation, but this medication is irritating and its use has been associated with airway bleeding. Selective embolization of aberrant intrapulmonary thoracic duct channels is extremely effective in decreasing symptoms of plastic bronchitis in patients who have lymphatic plastic bronchitis. In most cases, lymphatic ablation leads to a complete cure.⁷⁶

In patients with eosinophilic plastic bronchitis, systemic steroids, often given as pulse steroids, or inhaled heparin has been of some benefit. There are unpublished reports that some of the anti-eosinophil biologics used to treat severe asthma may be highly effective.

Cystic Fibrosis

CF is a hereditary disease characterized by impaired function of the CFTR protein. There is chronic airway infection, often with *Pseudomonas* and other gram-negative organisms. There is also chronic airway inflammation; infection and inflammation together lead to bronchiectasis, progressive pulmonary function decline, and eventually death. Although there may be mucus hypersecretion in CF, it is now known that with established CF bronchiectasis, the airway secretions contain very little intact mucin and obstruction appears to be due to DNA-actin polymers. The airways in CF are almost entirely filled with pus derived from neutrophil degradation and neutrophil extracellular traps. The decreased intact mucin in CF sputum may be related to chronic bacterial infection by *Pseudomonas aeruginosa* and breakdown of mucins by proteases derived from neutrophils or bacteria.^{61,77}

It is unclear how abnormal CFTR function leads to chronic infection and inflammation. Airway epithelia in CF have excessive absorption of Na^+ compared with normal epithelia. There is a limited ability for the epithelial cells to secrete Cl^- through the Cl^- CFTR channels (see Fig. 9.6) stimulated by cAMP. The result of excessive Na^+ absorption and limited Cl^- secretion may lead to decreased water and increased reabsorption of the periciliary fluid, the so-called “dehydration” hypothesis.⁷⁸ As an alternative, or complementary hypothesis, the “acidification” hypothesis notes that the CFTR protein is also impaired from secreting bicarbonate, leading to a more acidic airway secretion, and this acidification can both increase secretion viscosity and impair host defense.^{56,79,80} Abnormal phospholipids and surfactant degradation in CF secretions may also increase sputum adhesion and stickiness by altering surface properties of the secretion.³ CF sputum is bio-physically similar to bronchiectasis sputum.⁸¹

Physical Properties of Mucus

The biochemical composition and structure of mucus determine its physical properties, which influence the effectiveness of mucus transport.

KEY POINT

Physical properties of mucus include viscosity, elasticity, cohesivity, and adhesivity.

Surface Forces

Adhesion refers to forces between unlike molecules; also called “stickiness.” In the airway, adhesive forces refer to the attractive forces between the mucus and airway surface. Adhesion reduces the ability to clear secretions by airflow (cough).⁸² Mucokinetic agents are either **abhesives**, such as surfactant, which reduces the adhesivity of secretions, or agents that increase the power of airflow and cough. Mucolytics may work, in part, by severing the bonding of mucus to the epithelium, reducing inertial (frictional) adhesion.

Viscoelasticity and Cohesivity

Cohesion refers to forces between like molecules. Cohesive forces result from the elongation of the mucus macromolecule. A property of spinnability has been described as a surrogate measure of cohesivity.

Rheology or Viscoelasticity

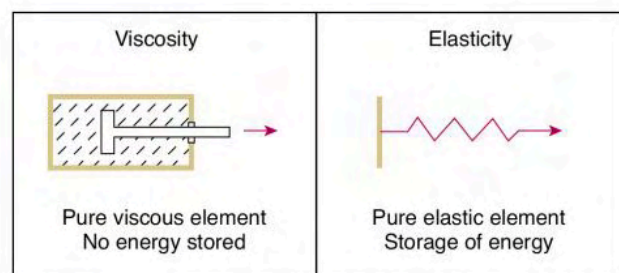
Rheology is the study of the dynamic deformation and flow of matter. The rheologic behavior of mucus describes the way it responds to applied force (stress). Viscosity is a property of liquids and describes the energy loss from the applied stress by deforming the liquid. Elasticity is a property of solids and describes energy stored by the solid with applied stress. It is important to understand that viscosity and elasticity are not constant measurements but vary with the rate and intensity of the applied stress. Thus, we describe either a range of viscosity measurements or, more commonly, quasistatic viscosity at a controlled stress. A gel, like airway mucus, has both viscous (liquid) and elastic (solid) properties. There is no single measurement that can be called “viscoelasticity.”

Viscosity, or loss modulus, is the resistance of a fluid to flow. The viscous properties of an ideal or Newtonian liquid can be described by the loss modulus G'' . **Elasticity**, or storage modulus, is the ability of a deformed material to return to its original shape. Ideal or Hookean solids store energy during deformation, and this energy is available when the force is removed. The properties of an ideal solid can be described by the storage modulus G' . The complex modulus (G^*) is the vectorial sum of viscosity and elasticity; this is also called the mechanical impedance. Fig. 9.7 illustrates the concept of viscosity and of elasticity.^{83–85}

Mucus as a Viscoelastic Material

The mucus gel is a viscoelastic material and responds to an applied stress as a fluid and as a solid. As a solid, a gel has elastic deformation, storing energy with applied force (e.g., ciliary beating), and as a liquid, a gel flows under applied force (e.g., extrusion from submucosal glands). As the tips of the cilia contact the gel during the forward power stroke, the gel is stretched, and its elastic recovery causes it to snap forward. At the same time, the mucus gel flows forward as a liquid under the forward beat of the cilia.

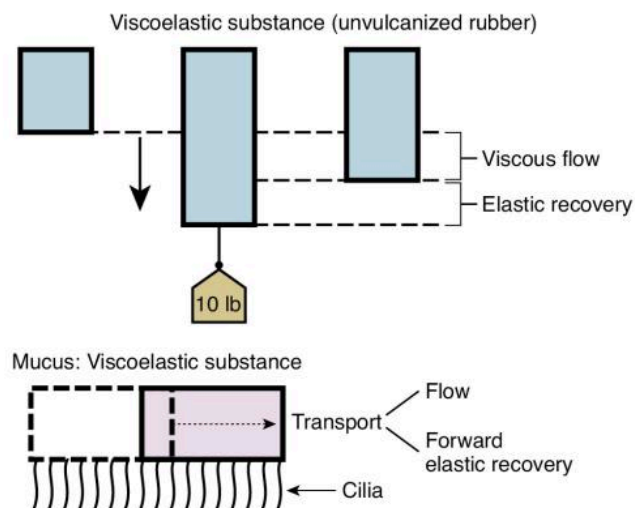
This model of gel transport is seen in Fig. 9.8, using unvulcanized rubber as an example of a viscoelastic substance. If such a rubber strip is loaded on one end with a weight and allowed to hang, it would initially stretch as an elastic solid. If the applied force remains, the strip would slowly elongate because of its viscosity (i.e., the rubber would “flow”). After removing the weight, the rubber recovers most of the elastic elongation because of stored energy, but it would not recover the entire length because of flow. Mucus behaves similarly. Mucociliary transport results from flow and forward elastic recovery. For this reason, the physical properties of viscosity and elasticity are important for efficient transport of respiratory secretions. Normal mucus generally has a relatively



Viscosity: Resistance to flow.

Elasticity: Property of deforming under force, resuming shape.

• Fig. 9.7 Illustration of concepts of viscosity and elasticity.



• **Fig. 9.8** Illustration of viscous and elastic properties affecting the movement of viscoelastic substances, such as unvulcanized rubber and mucus.

low viscosity, and its elasticity is high enough to provide forward propulsive energy.

Spinnability (Cohesivity) of Mucus

The ability of mucus to be drawn out into threads was initially identified for cervical mucus; it was termed *spinnability* and described in the German literature as *Spinnbarkeit*. The property of spinnability was subsequently studied by Puchelle and colleagues⁸⁶ for respiratory mucus. They used a device to stretch mucus vertically at a constant rate and measured the spinnability of a mucus thread as the maximal length to which the thread could be drawn before breaking. In general, there was a significant and positive correlation between spinnability of mucus and its mucociliary transport rate. Spinnability was found to increase with increasing elasticity. Spinnability and mucus transport were also found to decrease as the purulence of sputum from CB patients increased.

Spinnability gives information about internal cohesion forces in mucus. *Cohesivity* is defined as interfacial tension multiplied by

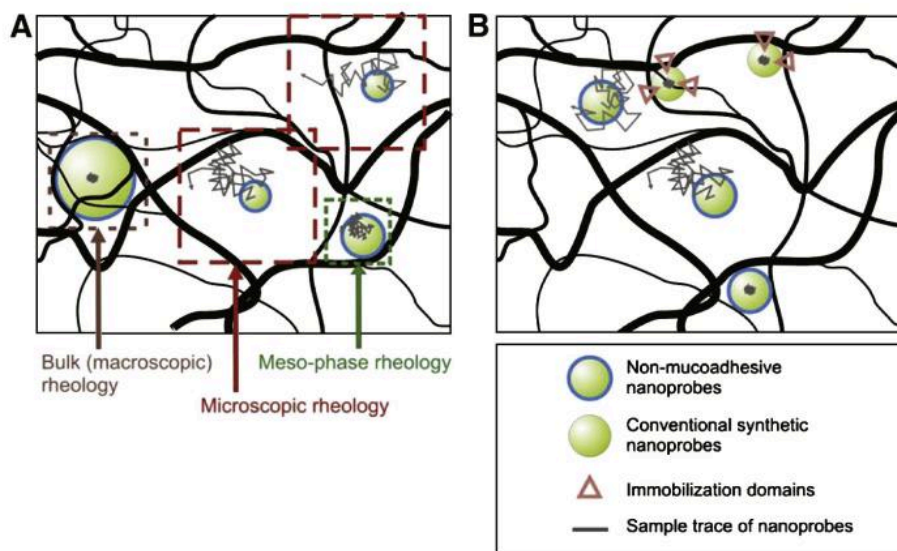
the new area created after a test substance is pulled apart and can be approximated by measuring spinnability. *Tenacity* is defined as the product of cohesivity and adhesive work. Tenacity is one of the strongest determinants of the ability of sputum to be cleared by cough. The greater the tenacity of sputum, the poorer the cough clearability.

Macro- and micro-rheological techniques are used to evaluate the viscoelastic properties of mucus such as storage modulus (G'), loss modulus (G''), and viscosity (η).⁴⁷ Mucus bulk rheology has a significant impact on normal barrier functions and lubrication efficiency. Macrorheology is measured by applying strain to a mucus material and its bulk stress response is noted, whereas for microrheological study, different sized probes are embedded in the mucus and transport measured to evaluate the material properties.⁸⁷ At macroscopic scale, mucus is a viscoelastic gel and its bulk rheology is characterized by a non-Newtonian behavior, where the rheology changes as a function of shear stress, rate of shear, and length scale.⁴⁷ At low shear rates, the viscosity of mucus is 10^4 – 10^6 times higher than that of water and exhibits shear thinning as shear rates increase.

Since mucus has a heterogenous structure, it allows diffusion of some proteins and smaller particles, while particles larger than the length scale of mucus microstructure may have limited diffusion through the mucus (Fig. 9.9).^{88,89} Microrheology of mucus provides information on the mucus mesh size and fluids present within the mucus mesh.⁴⁷ Techniques have been developed to characterize the microrheology of mucus secretions, with multiple particle tracking being the most commonly used.^{90–92} Using particle tracking, complex shear modulus, G' and G'' are calculated as explained in details by Lai et al. 2009.⁴⁷ The phase angle (δ) determines whether the mucus is a viscoelastic solid ($\delta < 45^\circ$, $G' > G''$) or a viscoelastic liquid ($\delta > 45^\circ$, $G' < G''$).⁹³

Non-Newtonian Nature of Mucus

Evaluation of mucus properties is complicated by the fact that mucus exhibits non-Newtonian rheology. A non-Newtonian gel, such as mucus, has changing viscosity with varying applied force (shear rate). As the shear rate increases, the apparent viscosity of



• **Fig. 9.9** Schematic representation of the length scale dependence of viscosity in a nanoscopically heterogeneous fluid. (From Lai SK, Wang YY, Wirtz D, et al. [2009]. Micro- and macrorheology of mucus. *Advanced Drug Delivery Reviews*, 61, 86.)

mucus usually decreases. Some mucus exhibits a sudden collapse of viscous behavior at high applied stress; this is called *apparent yield stress*. Sputum that yields may be more easily cleared by cough.⁹⁴ These changes in viscosity are consistent with rupture or change of the macromolecular chains and cross-linking network of the gel. Mucus can also be *thixotropic*—stable at rest but becoming more fluid with applied force and then thickening again when stress is removed. A common thixotropic solution is house paint.

Because of its non-Newtonian behavior, evaluation of the properties of mucus and of the effect of drugs on those properties is complicated and must be performed under standardized conditions of dynamic shear rate and across the linear portion of the stress-strain curve. Otherwise, interpretation of research findings on mucus viscosity is inaccurate.^{58,95} Many review articles and compendia are devoted to the physiology of mucus secretion in the lung and the nature of mucus.^{7,10,14,18,60,96–99}

Mucoactive Agents

CLINICAL CONNECTION

Three drugs are currently used in the United States to modify airway secretions: *N*-acetyl cysteine (NAC), dornase alfa, and hypertonic saline.

At the time of this edition, three drugs have been used in the United States as an aerosol, to treat abnormal pulmonary secretions: NAC, dornase alfa, and 7% saline. The first two of these drugs are considered mucolytic in action, disrupting disulfide bonds in mucus (NAC) or enzymatically breaking down DNA in airway secretions (dornase), although there is no evidence that NAC is mucolytic *in vivo* or that it is therapeutically effective. Inhalation of 7% hypertonic saline as an aerosol is now recommended as part of the treatment regimen for CF. Bicarbonate solutions for aerosol instillation are not approved for use but are currently being studied as possible therapy for CF as bicarbonate secretion is also impaired by the abnormal CFTR protein. Table 9.3 summarizes the spectrum of agents in current use with the potential to improve mucus clearance.

TABLE 9.3 Drugs Used or Under Investigation as Aerosol Mucoactive Medications

Drug	Description
Dornase alfa	Peptide mucolytic
Hyperosmolar saline	Expectorant
Dry powder mannitol	Expectorant
Thymosin β_4	Peptide mucolytic
Surfactants	Abhesive, mucokinetic
β Agonists	Secretagogues; potentially mucokinetic if airflow increases
Anticholinergic agents	Mucoregulatory
Corticosteroids	Mucoregulatory
Dapsone	Mucoregulatory

Mucolysis and Mucociliary Clearance

Mucolytic agents decrease the elasticity and viscosity of mucus. Because elasticity is crucial for mucociliary transport, mucolytics have the potential for a negative effect on normal physiologic mucus clearance. Reduction of mucus gel to a more liquid state *may* facilitate aspiration of secretions with the use of suction catheters.¹⁰⁰ The status of mucolytic agents in pulmonary disease has been reviewed at several conferences on the scientific basis of respiratory care.^{101–103}

The therapeutic options for controlling mucus hypersecretion are outlined as follows:

1. Remove causative factors where possible
 - a. Treat infections
 - b. *Avoid all tobacco smoke exposure*
 - c. Avoid pollution and allergens
2. Improve tracheobronchial clearance
 - a. Use bronchodilators if these are able to increase expiratory airflow (i.e., in asthma)
 - b. Use bronchial hygiene measures
 - (a) Cough, deep breathing
 - (b) Chest physical therapy (CPT)
 - (c) Other airway clearance devices and maneuvers
 - a. Improve airflow by exercise and nutrition rehabilitation
3. Use mucoactive agents when indicated

Mucolytics and Expectorants

Classic mucolytics reduce mucins by severing disulfide bonds or charge shielding.

N-Acetyl-L-Cysteine and Other Thiol Mucolytics

Indications for Use

CLINICAL CONNECTION

Acetylcysteine does *not* improve mucus clearance when given as an aerosol or when given orally and should not be used as a mucoactive medication.

As a mucolytic, NAC has been used in conditions associated with viscous mucus secretions. A second use of NAC is as an antioxidant antidote to reduce hepatic injury with acetaminophen overdose.¹⁰⁴ The drug is given orally for this use. Despite *in vitro* mucolytic activity and a long history of use, there are no data showing that aerosolized NAC is effective therapy for any lung disease,¹⁰⁵ and its use may be harmful. This harm may be due, in part, to NAC selectively depolymerizing the essential mucin polymer structure and leaving the pathologic polymers of DNA and F-actin intact. Because there are no data that show NAC to be effective for lung disease and because of the risk of side effects, we do not recommend its use.

Mode of Action

NAC disrupts the structure of the mucus polymer by substituting free thiol (sulfhydryl) groups for the disulfide bonds connecting mucin proteins. The substituted sulfhydryl group in mucus does not provide a bond for cross-linking between strands. When in physical contact with mucus, NAC begins to reduce viscosity, and mucolytic activity increases with a higher pH of 7 to 9. The solution of NAC contains a chelating agent, ethylenediamine

tetraacetic acid (EDTA). A light purple solution indicates metal ion removal. It is suggested that opened vials of the drug be stored in a refrigerator and discarded after 96 hours to prevent contamination. Additional details in the manufacturer's package insert should be reviewed.

Hazards

The most serious potential complication with NAC is bronchospasm caused by its acidity (pKa 2.2). Bronchospasm is more likely in asthmatic patients. Other complications include stomatitis, nausea, and rhinorrhea. Mechanical obstruction of the airway can occur, and suction should be available with artificial airways. The disagreeable odor of NAC is due to the release of hydrogen sulfide, and this may provoke nausea or vomiting. In prolonged nebulization, the manufacturer suggests that after three-fourths of the solution is nebulized, the remaining one-fourth should be diluted with an equal volume of sterile water to prevent the formation of a highly concentrated residue that could irritate the airway. An aerosol of NAC may leave a sticky film on the hands or face.

Incompatibility With Antibiotics in Mixture

NAC is incompatible in mixture with the following antibiotics:

- Sodium ampicillin
- Amphotericin B
- Erythromycin lactobionate
- Tetracyclines (tetracycline, oxytetracycline)
- Aminoglycosides

Incompatibility is taken to mean the formation of a precipitate; a change in color, clarity, or odor; or other physical or chemical change. NAC is reactive with numerous substances, including rubber, copper, iron, and cork. A complete list of incompatibilities for NAC can be found in the manufacturer's literature.

Dornase alfa (Pulmozyme)

CLINICAL CONNECTION

Dornase alfa is indicated only for clearance of purulent secretions in *cystic fibrosis (CF)*.

Peptide mucolytics reduce extracellular DNA and F-actin polymers. Dornase alfa is a recombinant form of the human DNase I enzyme, which digests extracellular DNA. In February 1994, the US Food and Drug Administration (FDA) approved dornase alfa for general use in treating the abnormally tenacious DNA-containing sputum of CF.

Dornase alfa was the first approved mucoactive agent for the treatment of CF. Dornase alfa is safe and effective in patients with more severe pulmonary disease, defined as a forced vital capacity (FVC) less than 40% of the predicted value.¹⁰⁶ Efficacy has not been shown for therapy of acute exacerbations of CF lung disease or for the treatment of other chronic airway diseases.¹⁰⁷ Several studies have shown no efficacy when used to treat non-CF bronchiectasis, and the use of dornase decreased pulmonary function and increased the risk of death in adults with non-CF bronchiectasis.¹⁰⁸ Dornase has not been shown to improve pulmonary function in children with severe asthma or in adults with COPD and increases the risk of death when given to adults with COPD. This worsening of disease may be due to the fact that secretions in COPD are composed primarily of mucin and related proteins,¹⁰⁹ whereas CF airway secretions primarily contain neutrophil-derived pus.⁵⁹

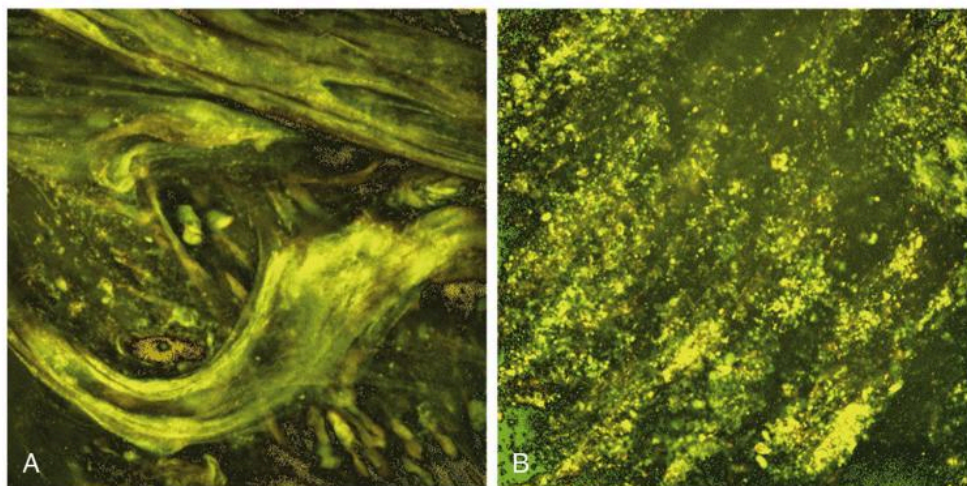
Indication and Use in Cystic Fibrosis

Dornase alfa is indicated for the management of CF to reduce the frequency of respiratory infections and to improve or preserve pulmonary function in CF patients. The bulk and surface properties of respiratory secretions in CF are due to the presence of DNA from dying cells such as neutrophils or neutrophil extracellular traps (NETs) present during chronic respiratory infections and to surfactant phospholipid hydrolysis by products of inflammation. In the presence of infection, neutrophils move into the airways and release DNA.^{110,111} DNA in secretions may also contribute to reduced effectiveness of aminoglycoside antibiotics, perhaps by binding the antibiotic to the polyvalent anions of the DNA.

Mode of Action

Dornase alfa reduces the viscosity and adhesivity of infected respiratory secretions when given by aerosol (Fig. 9.10).

When mixed with purulent sputum from subjects with CF, dornase alfa reduced the viscosity and adhesivity of the sputum.¹⁰⁶



• **Fig. 9.10** Illustration of the mode of action of dornase alfa in reducing DNA polymers in CF sputum. Confocal micrograph showing CF sputum stained (with YOYO-1) for DNA before (A) and after (B) treatment with dornase alfa in vitro. The long DNA polymers are degraded after dornase treatment.

This reduction was associated with a decrease in the size of the DNA polymers in the sputum. The change in sputum viscosity with the addition of dornase alfa is dose dependent, with greater reduction occurring at higher concentrations of the drug.

Dose and Administration

The aerosol product of dornase alfa is available as single-use ampoule, with 2.5 mg of drug in 2.5 mL of clear, colorless solution. The solution should be refrigerated and protected from light. The usual dosage is 2.5 mg daily, delivered by one of the following approved nebulizers: Hudson RCI UP-DRAFT II OPTI-NEB nebulizer with tee (Teleflex Medical, Research Triangle Park, North Carolina) or the Acorn II nebulizer (Vital Signs, Totowa, New Jersey) with a DeVilbiss Pulmo-Aide compressor (Sunrise Medical, Carlsbad, California), or the PARI LC PLUS nebulizer (PARI Respiratory Equipment, Midlothian, Virginia) with PARI Inhaler Boy compressor.¹¹² Although other nebulizer systems may perform suitably in nebulizing dornase alfa, this should not be assumed without testing. Optimal delivery of the enzyme requires a nebulizer system capable of suitable aerosol generation (i.e., particle size and quantity). This is especially important when administering expensive drugs or aerosol medications with a narrow therapeutic index.

Adverse Effects

Side effects of dornase differed little from those of placebo in CF clinical trials, and the discontinuation rate was similar for dornase (3%) and the placebo (2%). Common side effects with use of the drug have included voice alteration, pharyngitis, laryngitis, rash, chest pain, and conjunctivitis. Other, less common side effects reported include respiratory symptoms (cough increase, dyspnea, pneumothorax, hemoptysis, rhinitis, and sinusitis), flu syndromes and malaise, gastrointestinal obstruction, hypoxia, and weight loss. Contraindications include hypersensitivity to the medication. On the other hand, inhaled dornase has not been shown to be effective for treating any other lung disease and is most likely harmful when used to treat pneumonia, COPD, asthma, burn injury, or non-CF bronchiectasis.

Clinical Application and Evaluation

The intent of treatment with dornase alfa is to preserve or improve lung function in CF while reducing the frequency and severity of respiratory infections by improving secretion clearance. A reduction in use of intravenous antibiotic therapy and the need for hospitalizations has also been reported. Evaluation of drug treatment is based not only on lung function but also on a reduction in the number and severity of infectious exacerbations and the need for antibiotics and hospitalization.¹¹³

Filamentous Actin-Depolymerizing Drugs: Thymosin β_4

Chronic inflammation is characterized by inflammatory cell necrosis and release of polymeric DNA, F-actin, and intracellular enzymes from neutrophils. These inflammatory products are present in the sputum from patients with CF. DNA and F-actin in the sputum copolymerize to form a rigid network that is entangled in the mucin gel. Peptide mucolytics degrade these filaments, although they leave the glycoprotein network relatively intact. Gelsolin, an 85-kDa actin-severing peptide, decreases the viscosity of CF sputum in a dose-dependent manner. However, clinical trials of this drug failed to show any benefit, most likely because of the large size and rigidity of the protein, which makes

it susceptible to degeneration with aerosolization. Thymosin β_4 , a much smaller peptide, decreases sputum cohesivity and viscosity in a dose-dependent and time-dependent manner.^{114,115} In vitro studies have shown that administration of F-actin-depolymerizing agents along with dornase alfa results in greater reduction in sputum cohesivity and viscoelasticity than administration of either agent alone.^{116,117} Actin-depolymerizing agents destabilize the actin–DNA filament network and increase the depolymerizing activity of dornase alfa on the DNA filaments.

Expectorants

CLINICAL CONNECTION

Potassium iodide and glycerol guaiacolate are considered *expectorants*, rather than mucolytics, but these drugs have not been shown to be effective for treating acute or chronic airway disease.

Iodide-Containing Agents

Iodide-containing agents (e.g., supersaturated potassium iodide [SSKI]) are generally considered to be **expectorants**. They are thought to stimulate the secretion of airway fluid. Iodopropylidene glycerol (IPG) may acutely increase tracheobronchial clearance as measured by radiolabeled aerosol in patients with CB.¹¹⁸ However, in a double-blinded crossover study in subjects with stable CB, therapy with IPG failed to show any improvement in pulmonary function, gas trapping, or sputum properties, and this medication has subsequently been taken off the market.¹¹⁹

Sodium Bicarbonate

Sodium bicarbonate (2%) is a base that has occasionally been used for direct tracheal irrigation or as an aerosol. The inflammation caused by bicarbonate is thought to draw water into secretions, but this has not been shown clinically. Local bronchial irritation may occur with a bronchial pH greater than 8.0. Sodium bicarbonate has not been shown to improve airway mucus clearance. However, in CF there is loss of airway bicarbonate transport with acidification of secretions. Aerosol bicarbonate is now being studied as a potential therapy for CF.

Guaifenesin (glycerol guaiacolate)

Guaifenesin is usually considered to be an expectorant rather than a mucolytic. It can be ciliotoxic when applied directly to the respiratory epithelium.¹²⁰ It is thought that the expectorant action of guaifenesin is mediated by stimulation of the gastrointestinal tract and not by systemic exposure to the drug.¹²¹

Guaifenesin has been approved as an expectorant by the FDA in a bilayer extended-release tablet (Mucinex, Reckitt Benckiser). A large study of this drug in adults with acute infectious bronchitis failed to show any significant differences in sputum volume, sputum properties, or symptom resolution compared with placebo.¹²² One study suggested that as an adjunctive therapy for patients taking antibiotics with upper airway infections, guaifenesin/pseudoephedrine shortened time to relief and improved symptoms for nasal congestion and sinus headache better than placebo.¹²³ Guaifenesin may cause nephrolithiasis.¹²⁴

Dissociating Solvents

Urea is a dissociating agent that can break ionic and hydrogen bonds. In mucin gels, urea disrupts the hydrogen bonds between the oligosaccharide side chains of the neighboring mucus molecules,

with subsequent decrease in the physical entanglements between the molecules and decreased viscosity of the mucus. Urea may also decrease the interaction between DNA molecules. Because the mucolytic action of urea occurs only at very high concentrations of urea (3 to 8 mol/L),^{125,126} it is inappropriate for clinical use.

Oligosaccharides

Oligosaccharide side chains constitute about 80% of the mucin structure. These hydrogen bonds are weak and can be disrupted by agents such as dextran, mannitol, and lactose. The lower-molecular-weight fractions of dextran are primarily responsible for the mucoactive effects of dextran. Furthermore, an osmotic effect of dextran with increased hydration of the mucus could possibly improve clearance of secretions. Dextran administration via aerosol has been shown to improve tracheal mucus velocity in dogs.¹²⁷

Mannitol administered by dry-powder inhaler (DPI) (Bronchitol) has been approved in Australia and Europe for treatment of CF and non-CF bronchiectasis. Clinical studies have shown Bronchitol to be safe and well tolerated for treating patients with CF or bronchiectasis. However, because some children with CF have acute decrease in pulmonary function (bronchial hyperreactivity) with inhaled mannitol, similar to hyperosmolar saline,¹²⁸ it is important to pretreat with a short-acting bronchodilator before use. Aridol, a dry powder inhaled mannitol is approved in the use for the use in bronchial challenge testing in the pulmonary function laboratory.

The charged oligosaccharide heparin has a greater mucolytic and mucokinetic capacity compared with the neutral oligosaccharide dextran. Heparin may cause hydrogen bond disruption and improved ionic interactions. Aerosolized low-molecular-weight heparin shows promise in the treatment of asthma, presumably by interfering with antigen-receptor binding.¹²⁹ Aerosolized heparin has also been used effectively to prevent airway cast formation in persons with plastic bronchitis.

Mucokinetic Agents

KEY POINT

Other agents modifying airway secretions include inhaled anticholinergics such as atropine, tricyclic nucleotides, phospholipids, antiproteases, and gene therapy.

Mucokinetic agents increase cough clearance by increasing expiratory airflow or by reducing sputum adhesivity and tenacity.

Bronchodilators

Beta agonists increase ciliary beat frequency, but this has no significant effect on mucus clearance. Of greater importance is that these medications can increase expiratory airflow in individuals with an asthmatic component of airway disease.¹³⁰ However, airway muscle relaxation can also decrease expiratory airflow by producing dynamic airway collapse in persons with “floppy airways,” such as those with bronchomalacia or tracheomalacia.¹³¹ Beta agonists are also weak mucus secretagogues and therefore can *potentially* increase airway obstruction.

Surface-Active Phospholipids

Surfactant is produced in the conducting airways and in the alveoli and is important for mucociliary and cough clearance. A

surfactant sheet between the periciliary fluid and the mucus gel prevents airway dehydration, permits mucus spreading on extrusion from glands, and allows efficient ciliary coupling with mucus and, more importantly, ciliary release from mucus once kinetic energy is transmitted. With airway inflammation, surfactant can be degraded by phospholipases, and inflammatory peptides can inhibit surfactant function further. In the absence of surfactant, mucus sticks to the epithelium, rendering cough less effective. There is loss of surfactant in the inflamed airway of patients with CB or CF.^{132,133}

It has been reported in a randomized, multicenter study that surfactant aerosol improves pulmonary function and sputum transportability in patients with CB and that this effect is dose dependent. No significant side effects were attributable to the surfactant therapy.¹³⁴ As a wetting and spreading agent, surfactant also has the ability to increase the lower airway deposition of other aerosol medications, such as dornase alfa or gene therapy vectors, and may increase small particle translocation through the mucus layer.¹³⁵

Mucoregulatory Medications

Another approach to reducing the burden of airway secretions is to decrease hypersecretion by goblet cells and submucosal glands. Medications that decrease mucus hypersecretion are referred to as **mucoregulatory agents**. These medications include antiinflammatory drugs such as corticosteroids, which are effective at decreasing the inflammatory stimulus that leads to mucus hypersecretion. Aerosolized indomethacin has also been used in Japan to treat patients with mucus hypersecretion.⁷¹

Anticholinergic medications are also used as mucoregulatory medications. Atropine is routinely given perioperatively to prevent laryngospasm and to decrease mucus secretion associated with endotracheal intubation. Atropine and its derivatives are mucoregulatory medications because they do not “dry” secretions or increase viscosity, but they do decrease hypersecretion that is mediated through muscarinic cholinergic stimulation. The quaternary ammonium derivatives of atropine, including ipratropium bromide and tiotropium, do not significantly cross the blood–airway barrier and, as such, their use is not associated with systemic effects of anticholinergic medications, such as flushing or tachycardia. Studies have also shown that the use of ipratropium is associated with a reduction in the volume of mucus secretion in patients with CB.¹³⁶ Tiotropium is now widely used in patients with CB and has also been approved for chronic therapy of asthma in patients 12 years of age and older.¹³⁷ Tiotropium appears to be more effective in decreasing mucus secretion stimulated by neutrophil elastase than by the T2 (allergic) cytokine, IL-13.

The mucoregulatory medications include the macrolide antibiotics. These antibiotics were discovered over 60 years ago, and derivatives of erythromycin A have been widely used for the treatment of bacterial infection. Since the mid-1960s, data confirm that these medications also have immunomodulatory properties; they decrease hyperimmunity or inflammation to more normal and beneficial levels. The mechanism for these properties is different from that of corticosteroids.

The immunomodulatory and mucoregulatory properties of macrolide antibiotics have been exploited for the treatment of DPB, a chronic inflammatory airway disease with great morbidity and mortality when untreated. DPB has primarily been described in East Asia. The etiology is unknown, but the disease results in chronic sinobronchitis with mucus hypersecretion and

debilitation. Antibiotics and corticosteroids are ineffective for the treatment of DPB. By virtue of their immunomodulatory and mucoregulatory properties, the macrolide antibiotics have been shown to be the most effective agents for the treatment of DPB.¹³⁸ The 15-member azilide, but not the 14- or 16-member macrolides, is also highly effective for the therapy of CF airway disease.^{139,140} Macrolide mucoregulatory properties are now thought to be due to inhibition of ERK $\frac{1}{2}$,¹⁴¹ which is also in the common mucus secretory pathways.¹⁴²

Other Mucoactive Agents

Antiproteases

Patients with CF have increased activity of serine proteases on the respiratory epithelial surface. Neutrophils, when activated or degenerating, release proteases, such as elastase, that can directly damage epithelial cells and impair airway clearance. Neutrophil proteases cause a secretory response from submucosal glands with an increase in mucus production.¹⁴³

Intravenous administration or inhalation of α_1 -antitrypsin suppresses the activity of neutrophil elastase and restores the bacteria-killing capacity of neutrophils. Recombinant secretory leukocyte protease inhibitor (rsLPI), when given to a small number of CF patients at a dosage of 100 mg bid for 1 week, decreased neutrophil elastase and interleukin-8 in airway fluid. No significant side effects were reported.¹⁴⁴ It has also been reported that heparin has significant antiprotease activity, as well as activity against the important inflammatory peptide high-mobility group protein B1 (HMGB1).¹⁴⁵ These qualities may account for heparin's antiinflammatory properties and suggest that forms of heparin that do not increase the risk of bleeding may be effective for treating diseases like or plastic bronchitis.

Hyperosmolar Saline and Mannitol

For many years, sputum induction by hyperosmolar saline inhalation has been used to obtain specimens for the diagnosis of pneumonia. Hypertonic saline has been used as an irritant to induce cough. Hyperosmolar saline (7%) can improve mucociliary transport and lung function, thought to be largely due to the acute effects of inducing cough and hydrating airway surface fluid.^{146,147} In a pilot study, 58 CF subjects were randomly assigned to receive 10 mL of either 0.9% normal saline or 6% hypertonic saline twice daily by ultrasonic nebulization.¹⁴⁸ Spirometry was performed before treatment, at the end of 2 weeks of treatment, and 2 weeks after treatment. At the end of treatment, there was a significant increase in FEV₁ in the hypertonic saline group, with a return to baseline by 28 days. Despite pretreatment with 600 mcg of inhaled salbutamol (albuterol), several patients had an acute decrease in FEV₁ after inhaling hypertonic saline. Similarly, hyperosmolar dry powder mannitol (Bronchital, Pharmaxis) improves quality of life and pulmonary function in adult subjects with non-CF bronchiectasis and significantly improves the surface adhesivity and cough clearability of expectorated sputum.¹⁴⁹

Studies summarized in the *Cochrane Database of Systematic Reviews* confirm that the long-term use of inhaled hyperosmolar saline improves pulmonary function in patients with CF,^{146,150,151} and inhaled hyperosmolar saline or mannitol is beneficial in bronchiectasis.¹⁵² Although this therapy is readily available and inexpensive, it has been reported that hypertonic saline aerosol is not as effective as dornase alfa in the therapy of CF lung disease.¹⁵³ In

CF, hyperosmolar saline promotes mucus clearance with improvement in pulmonary function and a decrease in respiratory tract exacerbations.^{146,150} It is now recommended as part of the treatment regimen for this disease. It is important to note that in a study of COPD patients, there was no clinical improvement using hypertonic saline, but cough or bronchospasm occurred more frequently than in controls.¹⁵⁴

Gene Therapy

Gene transfer therapy represents a novel use for aerosols. Efforts in this arena have centered largely on complementary DNA transfer of the normal *CFTR* gene in CF patients. Gene transfer was first attempted by inserting the normal *CFTR* gene into a replication-defective adenovirus vector by bolus bronchoscopic delivery of the vector. An unanticipated host immune response to the vector led to reevaluation of this strategy.¹⁵⁵

For gene transfer to be effective, the vector and its package must be nonimmunogenic, stable to shear forces during aerosolization, and safe for transfected cells. The vector should not increase cell turnover. It should either stably integrate into the progenitor (basal) cell genome or be safe and effective with repeated administration and should be able to reach the cellular target of relevance. Part of the difficulty with CF is that its cellular target has not been clearly identified as the epithelial cell, ionocyte, submucous gland, or all of these. The amount of gene and vector and persistence in the airway must also be determined for each vector and delivery system.^{156,157}

Viral vectors that have been studied include *adenoviruses*, the *adeno-associated virus* (AAV), and the *lentivirus*. Adenoviruses naturally target the airway epithelium. These vectors are relatively safe but show inefficient gene transfer and induction of immune response upon repeated administration.¹⁵⁸ AAVs are very small organisms that require a “helper” virus to replicate. These viruses are capable of site-directed insertion into DNA, reducing the risk of insertional mutagenesis (initiating cancer by activation of an oncogene or inactivation of an oncogene suppressor).¹⁵⁹ In addition, AAV shows long-lasting gene expression, but small packaging capacity prevents transfer of larger genes.¹⁶⁰ Lentiviruses are retroviruses, such as human immunodeficiency virus (HIV). They are able to transfect cells that are not terminally differentiated, such as the basal or airway progenitor cell, but insertional mutagenesis is a risk.¹⁶¹ Gene transfer efficiency of lentiviral vector in the airway epithelium can be boosted by incorporation of certain surface proteins.¹⁶² Sendai virus (SeV) is a single-stranded RNA virus that contains sialic acid and cholesterol receptors on the apical surface, which makes them more efficient at transfecting airway epithelial cells.¹⁶³ The primary nonviral vectors studied to date have been cationic *liposomes*. These lipid capsules are able to form complexes with DNA and then enter cells. With the first generation of liposome vectors, the efficiency of gene transfer was poor; however, this has improved with newer systems.^{164,165}

Using Mucoactive Therapy With Physiotherapy and Airway Clearance Devices

A guideline for airway clearance therapies (ACT) in CF has been published recommending ACT for all CF patients for sputum clearance, maintaining lung function, and improving quality of life.¹⁶⁶ Although none of the therapies used has been shown to

be superior,¹⁶⁷ there may be advantages of particular therapies for individual patients. Patient preference should be considered with the anticipation that this will be associated with greater adherence to therapy.¹⁶⁶

Many physical factors affect secretion clearance. Cephalad airflow bias is responsible for the movement of mucus in airways during normal breathing.^{168–170} The narrowing of airways on exhalation increases the velocity and shearing forces in the airway, creating a cephalad airflow bias with tidal breathing. This bias is amplified during coughing, when increased transmural pressure causes the airways to fold and constrict, increasing airflow velocity further.¹⁷¹

In acute airway diseases leading to ciliary dysfunction, mucus hypersecretion, or both, cough is the primary mechanism for secretion clearance from the central airways, and cephalad airflow contributes increasingly to peripheral airway clearance. Cough is one of the most common respiratory complaints of patients seeking medical attention.¹⁷² During a normal cough, the expiratory airflow increases to a maximum along with narrowing of the intrathoracic airways. The narrowing of the airways is a product of high airflows and pressure differentials across the lung. Airflow velocity varies inversely with the cross-sectional area of the airways, creating high linear velocity, increased turbulence, high shearing forces within the airway, and high kinetic energy. These forces shear secretions and debris from the airway walls, propelling them toward the central and upper airway, where they are expectorated or swallowed. In COPD and bronchiectasis, narrowing airways may close prematurely, trapping gas, reducing expiratory flow, and limiting the effectiveness of the cough. Directed cough or huff (forced expiration with the glottis open) is a primary maneuver in these patients to improve secretion clearance.

Conventional CPT, consisting of chest percussion and directed cough produces greater expectoration than no treatment in patients with CF.¹⁷³ There is no evidence that postural or gravity-assisted drainage contributes to the effectiveness of airway clearance with CPT and there is a risk of increased gastroesophageal reflux when postural drainage is used.¹⁷⁴ Alternative methods of airway clearance (e.g., positive expiratory pressure [PEP], high-frequency chest wall compression [HFCWC]) all seem to work as well as CPT as long as they include directed cough. The choice between CPT and alternative methods mainly depends on patient preference and the response of the individual patient to treatment.¹⁷⁴

Insufflation-Exsufflation; Cough Assist

An insufflation-exsufflation device inflates the lungs with positive pressure followed by a negative pressure to simulate a cough.¹⁷⁵ The cycle begins with an inspiratory pressure of 20 to 40 cm H₂O for 1 to 2 seconds, followed by an expiratory pressure of 30 to 40 cm H₂O for 1 to 2 seconds. It can be used with an oronasal mask or attached to an artificial airway. Its primary application has been in patients with muscular weakness unable to cough unassisted. Although anecdotal reports suggest that routine use can decrease the frequency of pneumonia in patients with weak cough, there are no published randomized controlled clinical trials confirming this impression. Early work in COPD suggested benefits, but more recent evidence is lacking.¹⁷⁶

Active Cycle of Breathing and Forced Expiratory Technique Maneuver

The active cycle of breathing (ACB) technique involves a combination of breathing control, thoracic expansion control (deep

breaths), and forced exhalation from progressively increasing lung volumes. Although sometimes used by patients with CF, there are no controlled studies documenting benefits from this mode of airway clearance.¹⁷⁷

Forced expiratory technique (FET) consists of a breath taken in to mid-lung volume and air quickly exhaled by contracting the chest wall and abdominal muscles with the mouth and glottis kept open. The huff should not be a violent or explosive exhalation.^{178,179}

Autogenic Drainage

Autogenic drainage (AD) attempts to progressively increase airflow to move secretions without forced exhalation.^{180,181} This technique incorporates staged breathing, starting with small tidal breaths from expiratory reserve volume and repeating until secretions “collect” in the central airways. Patients are instructed to suppress cough. A larger volume of air is taken for a series of 10 to 20 breaths, followed by a series of even larger (approaching vital capacity) breaths, followed by several huff coughs. This technique requires a great deal of patient cooperation and is used only for patients older than 8 years of age and patients who have a good sense of their own breathing. AD can be difficult to teach and administer; application varies in different CF centers, and there are no randomized, controlled, clinical trials demonstrating the effectiveness of AD.

Exercise

Exercise increases sputum expectoration likely because of increased expiratory flow.^{182,183} Exercise seems to augment bronchial hygiene and should be encouraged.

Positive Airway Pressure

Positive airway pressure (PAP) techniques can be effective alternatives to CPT in expanding the lungs and mobilizing secretions. Evidence suggests that PAP therapy is more effective than incentive spirometry or intermittent positive pressure breathing (IPPB) in the management of postoperative atelectasis^{184,185} and more effective than HFCWC in treating CF.¹⁸⁶ Cough, FET, and other airway clearance techniques are components of PAP therapy.¹⁸⁷

Pursed-lip breathing is a procedure that can be used to relieve air trapping caused by collapse of unstable airways during exhalation. The resistance at the mouth during a pursed-lip exhalation transmits back pressure to splint the airways open, preventing compression and premature closure (similar to a fixed orifice resistor). Pursed-lip breathing represents a functional predecessor to modern device-based strategies of applying PEP to the airway. Expiratory positive airway pressure (EPAP) is produced as expired air passes through a fixed orifice or threshold resistor. However, continuous positive airway pressure (CPAP) has not been shown to improve mucus clearance.¹⁸⁸ By preventing expiratory airway collapse, PAP increases expiratory flow and may improve the distribution of ventilation throughout the lungs, via collateral intra-bronchiolar channels.^{189–191}

High-Frequency Chest Wall Compression

HFCWC has been shown to enhance secretion clearance. Shearing at the air-mucus interface could enhance tracheal mucus clearance during HFCWC, although there is no demonstrable effect on secretion rheology.¹⁹² Pilot studies suggest that dornase alfa is more effective for CF when given during HFCWC therapy than

when given before or after therapy.¹⁹³ Although there are now several HFCWC devices available in the US market, differences among these devices appear to be minimal and there are no studies demonstrating superior effectiveness of one device over another. Furthermore, none of these devices has been shown to be effective for therapy of any airway disease but CF.

Oscillatory Positive Expiratory Pressure

The Flutter mucus clearance device (Aptalis Pharma, Bridgewater, Connecticut) combines the techniques of PEP with high-frequency oscillations at the airway opening. The weight of the ball serves as a PEP device (approximately 10 cm H₂O) and the internal shape of the bowl allows the ball to flutter, generating oscillations of about 2 to 32 Hz, varying with the position of the device. The proposed mechanism of effect includes shearing of mucus from the airway wall by oscillatory action; stabilization of airways, preventing early airway closure; and facilitation of cephalad flow of mucus.

Although the Flutter has been available for over 20 years, little has been published on its efficacy.¹⁸⁷ In a small acute intervention study,¹⁹⁴ the amount of sputum expectorated by subjects with CF was greater than the amount expectorated with either voluntary cough or postural drainage. Another study reported that Flutter therapy was an acceptable alternative to conventional CPT in hospitalized patients with CF.¹⁹⁵ However, these results have not been confirmed by other studies, the relevance of expectorated sputum volume to clinical effectiveness is unproven, and most of the more recent studies of the Flutter have not shown it to be effective for airway clearance.^{196–200} Device performance varies with changes in expiratory flow and angle of inclination.²⁰¹ This lack of efficacy under “real-life” conditions may be due to the Flutter device being tiring to use correctly, which results in poor adherence. Similar devices such as the Acapella (Smiths Medical, St. Paul, Minnesota) and the Freuencer (Dymedso, Inc., Boisbriand, Quebec, Canada) may have less technique-dependent performance, but to date any improvement has yet to be reported. We generally do not recommend the use of these devices.

Intrapulmonary percussive ventilation (IPV) of the lungs involves the use of a pneumatic device called a Percussionator (Percussionaire Corp, Sandpoint, Idaho) with an aim to enhance the mobilization and clearance of retained secretions and deliver nebulized medications to the distal airways.²⁰² With IPV, the patient breathes through a mouthpiece that delivers high-flow minibursts at rates exceeding 200 cycles/min. During these percussive bursts of gas into the airway, continuous airway pressure is maintained while the pulsatile percussive intra-airway pressure progressively increases. Each percussive cycle is programmed by holding a thumb button for 5 to 10 seconds for the percussive inspiratory cycle and releasing the button for exhalation. Treatments of approximately 20 minutes are recommended by the manufacturer. Impaction pressures of 25 to 40 pounds-force per square-inch gauge (psig) are delivered at a frequency ranging from less than 100 up to 225 percussive cycles/min at 40 psig. Some small studies have reported comparable results with IPV and standard CPT,^{203–205} but there are no published long-term randomized controlled studies showing benefits.

Chest Wall Compression

HFCWC was first shown to improve mucus clearance more than 40 years ago and there are now several slightly different HFCWC

systems on the market; these are similar in operation, and probably in effectiveness. Although this technique is sometimes called high-frequency chest wall *oscillation*, this term is inaccurate and should not be used. These devices consist of a large-volume, variable-frequency air pulse delivery system attached to an inflatable vest that is worn by the patient so that it extends over the entire torso. Pressure pulses that fill the vest and vibrate the chest wall are controlled by the patient and applied during exhalation or throughout the respiratory cycle. Pulse frequency is adjustable from 5 to 25 Hz, with pressure varying from 28 mm Hg at 5 Hz to 39 mm Hg at 25 Hz. However, the compressions can be held at a single frequency between 10 and 15 Hz for the duration of therapy. Theoretically, rapid compression of the chest wall causes transient increases in airflow in the lungs to augment the movement of mucus. The frequency of compression (cycles per second) and flow bias (inspiratory versus expiratory) may influence effectiveness.^{206,207} The Vest has been shown to be effective for secretion clearance in patients with CF,^{208–210} but there are no randomized controlled studies showing effectiveness in other patients, and there may be risks to using this device when patients have a weak or ineffective cough.^{211,212}

KEY POINT

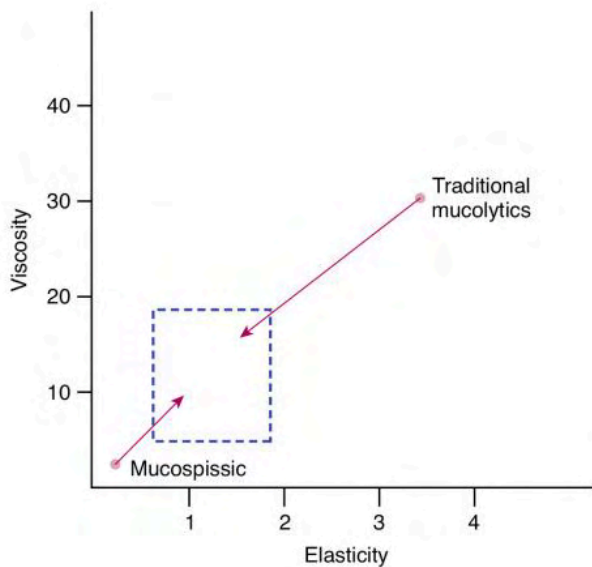
Patients with long-term problems of secretion management should be taught as many of these techniques as they can master for adoption in their therapeutic routines.²¹²

Future Mucus-Controlling Agents

In the past, mucolytics were targeted only at reducing the viscosity of mucus. In the context of the normal physiology of ciliary movement, logic suggests that thicker mucus would be moved more efficiently by ciliary contact and elastic recovery than would thin, low-viscosity solutions. The conceptual analogy is that of raking water—little transport occurs. This assumes mucus clearance is being optimized *physiologically*. Endotracheal aspiration of secretions by suction would be easier with low-viscosity mucus. Research supports the theory that elasticity is important for mucus transport.^{95,204}

It has been suggested that the treatment of bronchial hypersecretion would be better aimed at *normalizing* the rheologic properties of mucus to improve transport, rather than at simply lysing or liquefying bronchial secretions as is traditionally done. Indeed, cough clearance is enhanced by a cohesive and more viscous secretion that does not stick to the airway wall. In this sense, it is easier to shoot a solid pea from a pea shooter than it would be to shoot pea soup.

Purulent sputum has high elasticity *and* viscosity, and mucolytic agents such as dornase alfa might restore normal transport properties by reducing tenacity, viscosity, and elasticity. With low viscoelasticity (e.g., bronchorrhea), restructuring or cross-linking agents would increase viscosity and elasticity to improve transport. Such agents have been termed **mucospissic agents**.^{205,207} Drugs with mucospissic activity include tetracycline.²⁰⁴ The thickening effect of tetracycline can occur with oral and aerosol administration, although more so with direct aerosol. Tetracycline may bind to mucus proteins to increase viscosity and elasticity, although exact binding sites remain unclear. With adhesive sputum, mucokinetic agents that decrease tenacity and preserve viscoelasticity might be useful.



• **Fig. 9.11** Conceptual representation of an optimal range of viscosity and elasticity of mucus for mucociliary transport.

At present, no drugs are available in the United States as mucus-controlling agents that selectively modify viscosity or elasticity. Further investigation may produce clinically useful agents tailored to specific secretion problems, as illustrated in Fig. 9.11. A better understanding of adhesivity and cohesivity, the components of tenacity, has focused attention on control of the abnormal surface properties of mucus and sputum and their role in cough clearance.

RESPIRATORY CARE ASSESSMENT OF MUCOACTIVE DRUG THERAPY

Assessment of drug therapy for respiratory secretions is difficult. FEV_1 is relatively insensitive to changes in mucociliary clearance. Change in gas trapping or the rate of change in lung function over time may be a better way to assess effectiveness. In addition, during maintenance therapy the volume of sputum expectorated is variable from day to day and does not reflect effective therapy. Therefore, the following assessments should be performed.

Before Treatment

- Assess patient's adequacy of cough and level of consciousness to determine the need for mechanical suctioning or need for adjunct bronchial hygiene to clear airway with treatment, or whether treatment is contraindicated.

During Treatment and Short Term

- Instruct and then verify correct use of aerosol nebulization system, including cleaning.
- Assess therapy based on indication for the drug or device.
- Monitor airflow changes for adverse effects, such as a decrease in FEV_1 .
- Assess breathing pattern and rate.
- Assess patient's subjective reaction to treatment—that is, changes in breathing effort or pattern.
- Discontinue therapy if patient experiences adverse reactions.

Long Term

- Monitor number and severity of respiratory tract infections, need for antibiotic therapy, emergency visits, and hospitalizations.
- Monitor pulmonary function for improvement or slowing of the rate of deterioration.

General Contraindications

- If the FEV_1 is less than 25% of predicted, it becomes difficult to mobilize and expectorate secretions. Theoretically, with profound airflow compromise, secretion clearance could decrease.
- Use mucoactive therapy with caution in patients with severely compromised vital capacity and expiratory flow, such as in the presence of end-stage pulmonary disease or neuromuscular disorders.
- Gastroesophageal reflux and inability of the patient to protect the airway are risk factors for postural drainage.
- Mucoactive agents should be discontinued if there is evidence of clinical deterioration.
- Patients with acute bronchitis or exacerbation of chronic disease (e.g., CF and COPD) may be less responsive to mucoactive therapy, possibly because of infection and muscular weakness, which can reduce airflow-dependent mechanisms further.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify the mucolytic agents approved for inhalation as an aerosol in the United States—give the generic and brand names.
2. What is the mode of action for dornase alfa?
3. What is the clinical indication for use of dornase alfa?
4. What are contraindications to the use of mucolytic medications?
5. How do macrolide antibiotics affect mucus, and what are their indications for use?
6. How should dornase alfa be administered when high-frequency compression is used?
7. What is a common side effect seen with *N*-acetylcysteine (NAC) by aerosol?
8. What are the indications for the use of acetylcysteine?
9. How and when should bicarbonate aerosol or instillation be used?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 17-year-old woman with CF was admitted to your hospital with an acute respiratory infection (pulmonary exacerbation). She is pleasant, mature, and well informed concerning her disease. She complains of an increased cough, increased sputum production with some hemoptysis, and weight loss over the past 2 weeks.

History: She was diagnosed with CF at the age of 2 years because of failure to thrive and did well clinically until age 12. She has had a nasal polypectomy and had a G-tube placed for night feeding several years ago, which resulted in a weight gain of 30 lb (13.6 kg). She is chronically infected with resistant *Pseudomonas* and *Staphylococcus*, and she has grown atypical *Mycobacterium* in the past. She has been admitted with exacerbations of CF twice in the past year. She has been taking 300 mg of tobramycin (TSI) bid by aerosol at home regularly this year, with courses of oral ciprofloxacin when symptoms of respiratory infection surfaced.

Physical examination: Vital signs are as follows: temperature (T) 37.5°C, pulse (P) 110 beats/min and regular, respiratory rate (RR) 26 breaths/min, blood pressure (BP) 110/50 mm Hg. Oxygen saturation by pulse

oximetry (SpO_2) is 0.92 in ambient air. She has mild dyspnea while walking. Auscultation of the chest revealed crackles in all fields, with more in the right upper lobe. Extremities showed moderate digital clubbing with no cyanosis. She has a cough productive of greenish, thick sputum. No nasal polyps are visible to examination.

Laboratory: Electrolytes were normal, hemoglobin is 14.3 g/dL, hematocrit is 44%, and white blood cell count (WBC) is 13.4×10^3 cells/mm³. Chest radiograph shows diffuse chronic changes with thick interstitial markings consistent with bronchiectasis and a normal cardiac silhouette. There is an infiltrate in the right upper lobe. Her pulmonary function test results show the following:

Observed	% Predicted
Forced vital capacity (FVC)	72
Forced expiratory volume in 1 second (FEV_1)	55
Functional residual capacity	121

Hospital course: After her admission, she was treated for the next 21 days with intravenous antibiotics in addition to her usual medications of pancreatic enzymes and vitamin supplements, albuterol by aerosol before chest physical therapy (CPT), nocturnal tube feedings, and oxygen 1 LPM (liter per minute) at night. Her symptoms of dyspnea and her weight improved. She continues to have a productive cough with thick sputum, although the hemoptysis has disappeared. She is clinically stable and is ready to be discharged.

Using the SOAP method, assess this clinical scenario.

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10

Surfactant Agents

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CHAPTER OUTLINE

Physical Principles

- Surfactant
- Surface Tension
- Laplace's Law
- Application to the Lung

Clinical Indications for Exogenous Surfactants

Identification of Surfactant Preparations

- Composition of Pulmonary Surfactant
 - Lipids
 - Proteins
- Production and Regulation of Surfactant Secretion
- Types of Exogenous Surfactant Preparations
 - Natural and Modified Natural Surfactant
 - Synthetic Surfactant
 - Synthetic Natural Surfactant

Specific Exogenous Surfactant Preparations

- Beractant (Survanta)
 - Indications for Use
 - Dosage
 - Administration
- Calfactant (Infasurf)

Indications for Use

Dosage

Administration

Poractant Alfa (Curosurf)

Indications for Use

Dosage

Administration

Lucinactant (Aerosurf)

Hazards and Complications of Surfactant Therapy

- Airway Occlusion, Desaturation, and Bradycardia
- High Arterial Oxygen Values
- Overventilation and Hypocapnia
- Apnea
- Pulmonary Hemorrhage

Future Directions in Surfactant Therapy

Respiratory Care Assessment of Surfactant Therapy

- Before Treatment
- During Treatment and Short Term
- Long Term
- General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to surfactant agents.
2. List all available exogenous surfactant agents used in respiratory therapy.
3. Describe the mode of action for exogenous surfactant agents.
4. Discuss the route of administration for exogenous surfactant agents.
5. Recognize hazards and complications of exogenous surfactant therapy.
6. Assess the use of surfactant therapy.

KEY TERMS AND DEFINITIONS

Laplace's law Physical principle describing and quantifying the relationship between the internal pressure of a drop or bubble, the amount of surface tension, and the radius of the drop or bubble.

Prophylactic treatment Prevention of respiratory distress syndrome (RDS) in infants with very low birth weight and in infants with higher birth weight but who have evidence of immature lungs and are at risk for developing RDS.

Rescue treatment Retroactive, or "rescue," treatment of infants who have developed RDS.

Surface tension Attraction of molecules in a liquid–air interface, such as the liquid lining in lung tissue and the air, pulling the surface molecules inward.

Surfactants Agents that reduce surface tension.

This chapter reviews pharmacologic agents termed **surfactants**, which are intended to alter the surface tension of alveoli and the resulting pressures needed for alveolar inflation. The physical principles of surfactants and surface tension forces are reviewed as a basis for introducing agents that have been used or are currently used in respiratory care. The use of current exogenous surfactant agents in the treatment of respiratory distress syndrome (RDS) of the newborn is presented.

Physical Principles

KEY POINT

Surfactant agents regulate surface tension in films at gas–liquid interfaces. The interrelationship of surface tension, drop or bubble size, and pressure is described by Laplace’s law.

Exogenous surfactants are administered to replace missing pulmonary surfactant in RDS of the newborn. Surface-active agents act on liquids to affect surface tension. The following terms and concepts form the basis for an understanding of the application of surfactant preparations and their effects in the airway.

Surfactant

A surfactant is a surface-active agent that reduces surface tension. Examples include soap and various forms of detergent. Surfactants, or surface-active agents, have also been termed *detergents* for this reason.

Surface Tension

Surface tension is the force caused by attraction between like molecules that occurs at liquid–gas interfaces and holds the liquid surface intact. The units of measure for surface tension are usually dynes per centimeter (dyn/cm), indicating the force required to cause a 1-cm rupture in the surface film. Because the molecules in a liquid are more attracted to each other than to the surrounding gas, a droplet or spherical shape usually results (Fig. 10.1, A).

Laplace’s Law

Laplace’s law is the physical principle describing and quantifying the relationship among the internal pressure of a drop or bubble,

the amount of surface tension, and the radius of the drop or bubble (see Fig. 10.1, B). For a bubble, which is a liquid film with gas inside and out, Laplace’s law is as follows:

$$\text{Pressure} = (4 \times \text{surface tension})/\text{radius}$$

In alveoli, there is only a single air–liquid interface, and Laplace’s law is as follows:

$$\text{Pressure} = (2 \times \text{surface tension})/\text{radius}$$

Application to the Lung

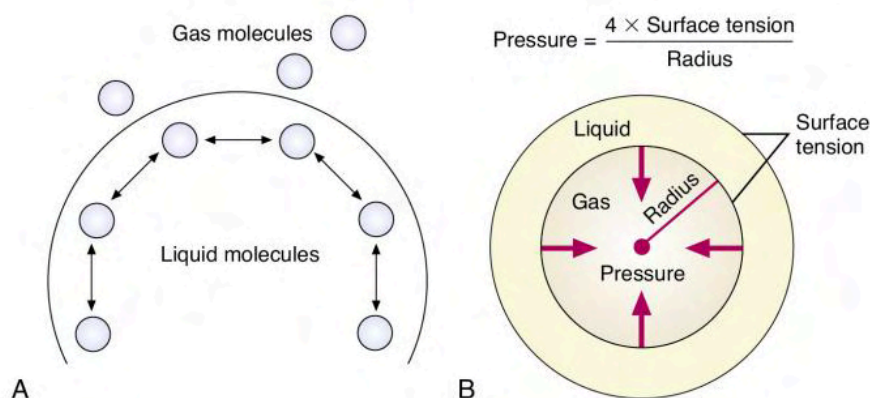
Because an alveolus has a liquid lining, surface tension forces apply. The higher the surface tension of the liquid, the greater is the compressing force inside the alveolus, which can cause collapse or difficulty in opening the alveolus. In foamy, bubbly pulmonary edema, the surface tension of the liquid allows the formation of the bubbly froth. In both cases—low compliance and pulmonary edema—lowering the surface tension eases alveolar opening or causes the foam bubbles to collapse and liquefy.

Clinical Indications for Exogenous Surfactants

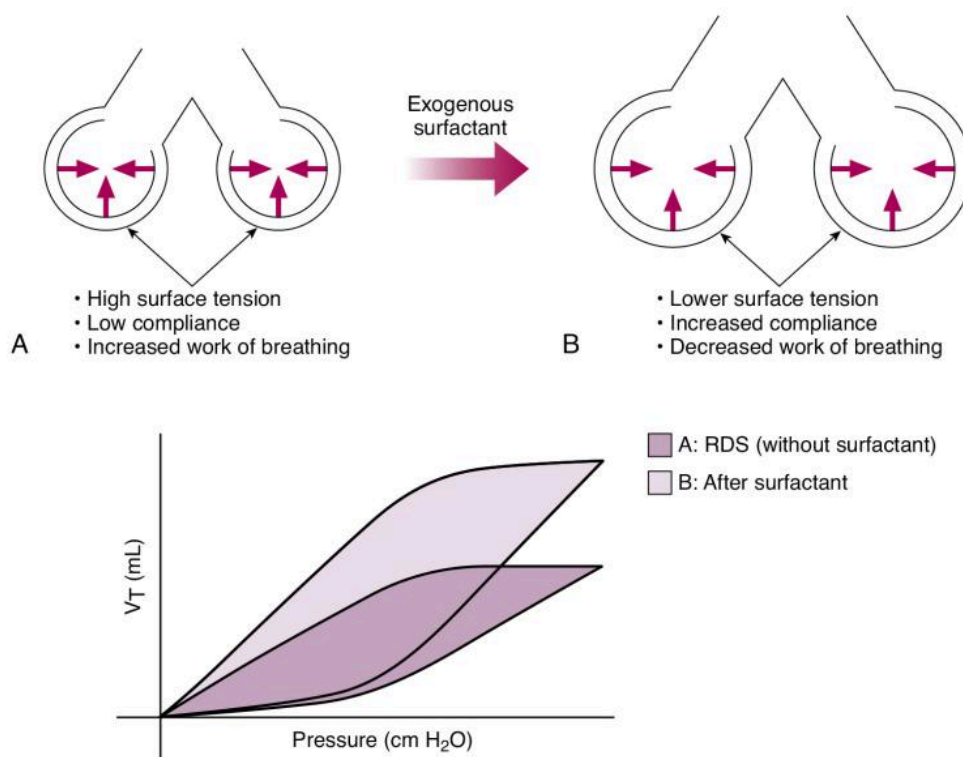
Exogenous surfactants are clinically indicated for the treatment or prevention of RDS in the newborn. There are two such treatments:

- **Prophylactic treatment:** Prevention of RDS in infants with very low birth weight and in infants with higher birth weight but with evidence of immature lungs, who are at risk for developing RDS
- **Rescue treatment:** Retroactive, or “rescue,” treatment of infants who have developed RDS

The basic problem in RDS is lack of pulmonary surfactant as a result of lung immaturity. This lack of pulmonary surfactant results in high surface tensions in the liquid-lined, gas-filled alveoli. Increased ventilating pressure is required to expand the alveoli during inspiration, which leads to ventilatory and respiratory failure in an infant without ventilatory support. This concept and the effect of an exogenous surfactant are shown in Fig. 10.2. Exogenous surfactants are also being investigated for efficacy in the treatment of acute respiratory distress syndrome (ARDS), acute lung injury (ALI), bronchopulmonary dysplasia (BPD), and meconium aspiration syndrome (MAS).¹ Exogenous surfactant is



• **Fig. 10.1 A**, The concept of like liquid molecules producing the attractive force resulting in surface tension. **B**, Laplace’s law illustrated for a bubble with two air–liquid interfaces. For alveoli (with only one air–liquid interface), the relationship is as follows: $\text{Pressure} = (2 \times \text{surface tension})/\text{radius}$.



• **Fig. 10.2** Top: **A**, Lack of pulmonary surfactant in respiratory distress syndrome (RDS) of the newborn results in high surface tension of the alveolar liquid lining and the need for high inspiratory pressures to expand alveoli. **B**, Exogenous surfactants reduce the high surface tension to reduce the pressures needed for alveolar expansion. Bottom: Graph illustrating change in the pressure–volume relationship without pulmonary surfactant (**A**) and after exogenous surfactant therapy (**B**). V_T , Tidal volume.

TABLE 10.1

Exogenous Surfactant Preparations Currently Approved for Use in the United States*

Drug	Brand Name	Formulation and Initial Dose
Beractant	Survanta	4- and 8-mL vial, 25 mg phospholipids/mL with 0.5–1.75 mg/mL triglycerides, 1.4–3.5 mg/mL free fatty acids, and <1 mg/mL protein Dose: 100 mg phospholipids/kg (4 mL/kg birth weight) in four divided doses by tracheal instillation
Calfactant	Infasurf	3- and 6-mL vial, 35 mg phospholipids/mL, with 0.65 mg proteins Dose: 3 mL/kg in two divided doses of 1.5 mL/kg by tracheal instillation
Poractant alfa	Curosurf	1.5-mL vial, 80 mg phospholipids, with 1 mg of proteins, or 3-mL vial, 160 mg phospholipids, with 2 mg of proteins Dose: 2.5 mL/kg (200 mg/kg) in two divided doses by tracheal instillation

*Individual agents are discussed in a separate section. Detailed information on each agent should be obtained from the manufacturer's drug insert.

not approved by the US Food and Drug Administration (FDA) for any application in adults or pediatrics.

Identification of Surfactant Preparations

Table 10.1 lists surfactant formulations that currently have FDA approval for general clinical use in the United States. Detailed differences between these formulations and details of their dosing and administration are discussed subsequently for each agent in separate sections.

KEY POINT

Three surfactant agents are currently used for treatment of neonatal RDS. Beractant (Survanta), calfactant (Infasurf), and poractant alfa (Curosurf) are modified natural agents.

The term *exogenous*, used to describe this class of drugs, refers to the fact that these are surfactant preparations from outside the patient's own body. These preparations may be obtained from other humans, from animals, or by laboratory synthesis. The clinical use of exogenous surfactants has been to replace the missing

pulmonary surfactant of the premature or immature lung in RDS of the newborn. These agents have also been investigated for use in ARDS and have been beneficial in improving oxygenation, although results have been inconsistent.^{2,3}

Composition of Pulmonary Surfactant

KEY POINT

Endogenous pulmonary surfactant is 90% lipids and 10% protein. The major phospholipid is dipalmitoylphosphatidylcholine (DPPC).

Pulmonary surfactant is a complex mixture of lipids and proteins (Box 10.1). The surfactant mixture is produced by alveolar type II cells. Their primary function, although not their only function, is to regulate the surface tension forces of the liquid alveolar lining. Surfactant regulates surface tension by forming a film at the

• BOX 10.1 Composition of Whole Surfactant From Bronchoalveolar Lavage Fluid (% by Weight)

Lipids (85%–90%)

- Phospholipids (approximately 90%)
- Phosphatidylcholine—half is dipalmitoylphosphatidylcholine (DPPC)
- Phosphatidylglycerol
- Phosphatidylethanolamine
- Phosphatidylserine
- Phosphatidylinositol
- Sphingomyelin
- Neutral lipids (10%)
- Cholesterol and others

Proteins (10%)

- Surfactant protein A (SP-A)
- Surfactant protein B (SP-B)
- Surfactant protein C (SP-C)
- Surfactant protein D (SP-D)

air–liquid interface. Surfactant reduces surface tension because it is compressed during expiration, reducing the amount of pressure and inspiratory effort required to reexpand the alveoli during a succeeding inspiration. The amount of extracellular (i.e., outside the type II cell) surfactant in animals is 10 to 15 mg/kg of body weight in adults and 5 to 10 times that in mature newborns.⁴ Fig. 10.3 illustrates the source, basic composition, and regulation of pulmonary surfactant in the alveolus. Each of the major components is described in the following sections.

Lipids

Lipids make up about 85% to 90% of surfactant by weight. The lipid component of surfactant is approximately 90% phospholipids, such as phosphatidylcholine, phosphatidylglycerol, sphingomyelin, and others, and 10% other lipids, most of which is cholesterol.⁵ Phospholipids have lipophilic and hydrophilic properties and can achieve low surface tensions at air–liquid interfaces. Phosphatidylcholine constitutes about 75% to 80% of the phospholipids in surfactant, and about half of this is dipalmitoylphosphatidylcholine (DPPC), which is also known as *lecithin*. DPPC is the surfactant component predominantly responsible for the reduction of alveolar surface tension. The hydrophilic choline residue of DPPC is associated with the liquid phase in alveoli, whereas the hydrophobic palmitic acid residue projects into the air phase.⁶

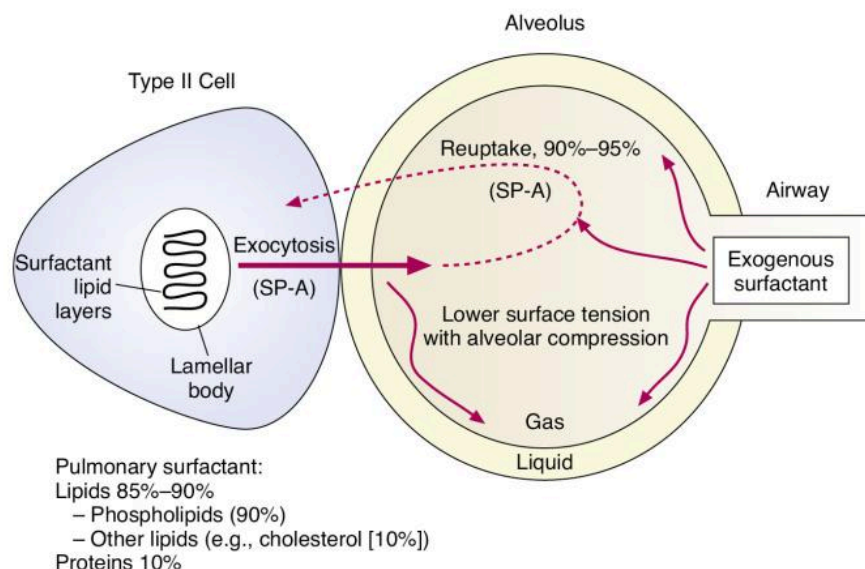
Proteins

KEY POINT

Surfactant-associated proteins, such as SP-A, SP-B, and SP-C, regulate the function of endogenous pulmonary surfactant.

The total protein portion of surfactant is about 10% by weight. Approximately 80% of this portion is contaminating serum proteins, and 20% is surfactant-specific proteins (SPs). Four SPs have been identified so far: SP-A, SP-B, SP-C, and SP-D.⁴ Proteins of the surfactant mixture are reviewed by Johansson et al.⁷

All components of surfactant are synthesized by the alveolar type II cell. The type I cell, which is the basic alveolar epithelial cell on 95% of the alveolar surface, has no known role in



• **Fig. 10.3** Production and reuptake of surfactant by type II cells. Exogenous surfactant is also taken up to become part of the surfactant pool for alveoli.

surfactant synthesis or metabolism. The type II cell also secretes other proteins, such as cytokines, growth factors, and antibacterial proteins, into the alveolar space. The role of the surfactant-associated proteins is well reviewed by Hawgood and Poulain⁸ and Possmayer.⁹

Surfactant Protein A (SP-A). SP-A is a high-molecular-weight, water-soluble glycoprotein. This protein is specific to surfactant; it has also been denoted as SP-35, apoprotein A, and SAP-35.⁴ SP-A seems to regulate secretion and exocytosis of surfactant from the type II cell and the reuptake of surfactant for recycling and reuse.

Surfactant Proteins B and C (SP-B and SP-C). SP-B and SP-C are low-molecular-weight, hydrophobic proteins that improve the adsorption and spreading of the phospholipid throughout the air-liquid interface in the alveolus.

Surfactant Protein D (SP-D). SP-D is the fourth protein identified in natural endogenous surfactant. Being a large, water-soluble protein, SP-D is like SP-A, although differences exist in their molecular configurations.⁸ There is no clear role for SP-D in surfactant function at this time, calling into question whether SP-D is correctly designated as a surfactant-associated protein.

Production and Regulation of Surfactant Secretion

CLINICAL CONNECTION

Exogenous surfactant enters the lamellar bodies to replace natural surfactant that is deficient.

The surfactant lipids are synthesized in the alveolar type II cells and stored in vesicles termed *lamellar bodies* (see Fig. 10.3). Surfactant in the lamellar bodies is secreted by exocytosis out of the type II cell and into the alveolus. The major stimulus for secretion of lamellar bodies into the alveolar space seems to be inflation of the lung, with a chemically coupled stretch response.¹⁰ SP-A and SP-B facilitate the formation of an intermediate lattice form of surfactant, termed *tubular myelin*, before it reaches the air-liquid interface. SP-C also helps to “break” the lipid layers of surfactant so that adsorption and spreading of the compound as a monolayer proceeds quickly through the air-liquid interface. Surfactant is converted to small vesicles, which can be taken back into the type II cell or taken into alveolar macrophages. The two major alveolar forms of surfactant are large surfactant aggregates (lamellar bodies and tubular myelin-like structures) and small vesicles or aggregates.¹¹ The secretion of surfactant material from the type II cell is estimated to be 10% of the intracellular pool every hour,¹² with an alveolar half-life between 15 and 30 hours.⁵ The constant secretion of surfactant is balanced by two clearance mechanisms: (1) endocytosis back into the type II cells and (2) clearance via degradation by alveolar macrophages.⁸ In addition, clearance can occur by degradation within the alveoli and by mucociliary removal and transport.⁵

A key feature of surfactant production, which is the basis for the success of replacement therapy with exogenous compounds, is the recycling activity in surfactant production. Most surfactant (90%–95%) is taken back into the alveolar type II cell, reprocessed, and secreted again. For this reason, exogenously administered surfactant is successful in replacing missing surfactant with one or two doses. The exogenous surfactant is taken into the type II cells and becomes the surfactant pool through the reuptake and recycling mechanism. The reuptake is regulated, at least partly, by

SP-A. SPs, or apoproteins, are critical for the surface-active functioning of surfactant and the metabolic regulation of the surfactant pool. This process is well described by Wright and Clements.⁶ The normal function of endogenous surfactant also depends on the structural organization of the compound. Smaller surfactant aggregates have less SP-A and are less surface active than larger aggregates.⁴

Pulmonary surfactant has also been found to contribute to host defense by increasing bacterial killing, modifying macrophage function, and downregulating the inflammatory response through decreased mediator release from inflammatory cells.¹³ Surfactant also enhances ciliary beat frequency and maintains patency of conducting airways.¹¹

Types of Exogenous Surfactant Preparations

Exogenous surfactant preparations can be placed into three categories. These categories and examples of each are listed in Table 10.2 and described in the following sections. A more complete technical description is given by Jobe and Ikegami.⁴

Natural and Modified Natural Surfactant

Natural surfactant is an apt descriptive term for the category of surfactants obtained from animals or humans by alveolar wash or from amniotic fluid. The large surface-active aggregates of natural surfactant are recovered from the fluid by centrifugation or simple filtration. Because these are natural surfactants, the ingredients necessary for effective function to regulate surface tension are present. Specifically, this includes the surface proteins needed for adsorption and spreading. Depending on the source, natural surfactants can be expensive and time consuming to obtain and prepare. In addition, there is concern over contamination with viral infectious agents or immunologic stimulation and antibody production in response to foreign proteins. Natural surfactant preparations are usually modified by the addition or removal of certain components. Examples of natural surfactants are given in Table 10.2.

The natural surfactant *beractant* (*Survanta*) is obtained as an extract of minced cow lung, supplemented with other ingredients, such as DPPC, palmitic acid, and tripalmitin. The modifications to the natural surfactant material are usually designed to improve functioning in the lung, reduce protein contamination, and provide sterility. Although *Survanta* contains the hydrophobic proteins SP-B and SP-C, the protein SP-A is missing, and this may shorten the duration of effect.

TABLE 10.2 Types of Surfactant Preparations and Examples

Category	Description	Examples
Natural	Surfactant from natural sources (human or animal) with addition or removal of substances	Survanta (bovine) Curosurf (porcine) Infasurf (bovine)
Synthetic	Surfactant that is prepared by mixing in vitro-synthesized substances that may or may not be in natural surfactant	None at present
Synthetic natural	Surfactant prepared in vitro by genetic engineering	None at present

Poractant alfa (Curosurf) is another modified natural surfactant, obtained as a pig lung extract. Calfactant (Infasurf) is a chloroform-methanol extract of fluid lavaged from calf lung; similar to Survanta, it contains the surfactant proteins SP-B and SP-C but not SP-A.¹⁴ Bovactant (Alveofact), not available in the United States, is an organic solvent extract of cow lung lavage containing 99% phospholipids and neutral lipids and 1% SP-B and SP-C.¹⁵

Synthetic Surfactant

Synthetic surfactants are mixtures of synthetic components. The characteristic feature of artificial surfactants is that none of the ingredients are obtained from natural sources, such as human, cow, or pig lung. Synthetic surfactants do not contain any of the surfactant proteins, including SP-B or SP-C, that are found in the natural preparations. A major advantage of this class of surfactant is its freedom from contaminating infectious agents and additional foreign proteins that may be antigenic to the recipient. A possible disadvantage is the lack of equivalent performance between the organic chemicals substituted for the naturally occurring surfactant proteins, such as SP-A, SP-B, or SP-C.

Synthetic Natural Surfactant

An ideal solution to the problems of natural and artificial surfactants would be genetically engineered surfactant produced by recombinant DNA technology. In such a preparation, the phospholipid, lipid, and protein ingredients of the natural surfactant aggregate would be produced by characterizing, via *in vitro* cloning, the gene or genes responsible for human surfactant. No such products are available for general use at this time, but work progresses on their development. The genes and amino acid sequence for each of the surfactant proteins have been characterized.^{16,17} A genetically engineered surfactant that closely resembles the structure and effect of natural human surfactant would be the ideal preparation.

Specific Exogenous Surfactant Preparations

CLINICAL CONNECTION

Exogenous surfactants are given either prophylactically in RDS or as rescue treatment.

Three exogenous surfactant preparations have been approved for general clinical use in the United States at the time of this edition.

CLINICAL CONNECTION

All surfactant preparations are administered differently. It is important to specifically review the administration of the surfactant preparation that is being given and to follow the policy and procedure of the institution.

Beractant (Survanta)

Beractant (Survanta) is considered a modified natural surfactant. It is a natural bovine lung extract mixed with colfosceril palmitate (lecithin), palmitic acid, and tripalmitin. These three ingredients are used to standardize the composition of the drug preparation and to reproduce the surface tension-lowering properties of natural surfactant. The ingredients are suspended

in 0.9% saline. The composition of beractant given in the product literature is described in Table 10.1. The extract from minced bovine lung contains natural phospholipids, neutral lipids, fatty acids, and the low-molecular-weight, hydrophobic surfactant proteins SP-B and SP-C. The hydrophilic, high-molecular-weight protein SP-A is not contained in beractant. SP-A helps regulate surfactant reuptake and secretion by alveolar type II cells. However, the addition of SP-A to beractant by Yamada et al.¹⁸ did not improve the biophysical activity (spreading and absorption) or the physiologic activity (lung compliance change) of the mixture.

Beractant is available in a vial containing 4 or 8 mL of suspension, with a concentration of 25 mg/mL, in a 0.9% sodium chloride solution. The suspension does not require reconstitution. This gives a maximal total dose of 100 mg (4 mL) or 200 mg (8 mL) of phospholipids in a single vial of 8 mL of suspension.

Indications for Use

Specific guidelines for use of beractant are as follows:

- Prophylactic therapy of premature infants less than 1250 g birth weight or with evidence of surfactant deficiency and risk of RDS: The agent should be given within 15 minutes of birth or as soon as possible
- Rescue treatment of infants with evidence of RDS: The agent should be given within 8 hours of age

Dosage

The recommended dose of beractant is 100 mg of phospholipids per kilogram of birth weight. Because there are 25 mg of phospholipids per milliliter in the beractant suspension, this is equivalent to a dose of 4 mL/kg of birth weight. For example, a 2000-g (2-kg) infant would require 8 mL, or the entire vial of suspension.

Repeat doses of beractant are given no sooner than 6 hours later if there is evidence of continuing respiratory distress. The manufacturer's literature recommends that manual hand-bag ventilation *not* be used for the repeat dose in place of mechanical ventilation. Ventilator adjustment may be necessary.

Administration

Beractant suspension is off-white to light brown in color. If settling has occurred in the suspension, the vial can be swirled gently, but it should not be shaken. The suspension is kept refrigerated and must be warmed by allowing it to stand at room temperature for at least 20 minutes. Artificial warming methods should not be used.

The calculated dose is given in four divided aliquots from a syringe and instilled into the trachea through a 5-French (5-F) catheter placed into the endotracheal tube (ETT). The catheter is removed, and the infant is manually ventilated for at least 30 seconds, or until stable, between doses. The remaining doses are given in similar fashion. During each aliquot, the infant is placed in a different position.

Unopened vials that have been warmed to room temperature may be returned to refrigerated storage within 8 hours. This should be done no more than once. Used vials should be discarded with any residual drug.

Calfactant (Infasurf)

Calfactant (Infasurf) is another modified natural surfactant preparation from calf lung (bovine). It is an organic solvent extract of calf lung surfactant obtained by cell-free bronchoalveolar lavage. The extract contains phospholipids, neutral lipids, and

the hydrophobic proteins SP-B and SP-C. The preparation is a suspension, which does not require reconstitution. Its composition is given in [Table 10.1](#). Each milliliter contains 35 mg of total phospholipids, including 26 mg of phosphatidylcholine, of which 16 mg is disaturated phosphatidylcholine, and 0.65 mg of proteins, which includes 0.26 mg of SP-B. The protein SP-A is not contained in the preparation. The formulation is heat sterilized and contains no preservatives.

Indications for Use

Specific guidelines for use of calfactant (Infasurf) are as follows:

- Prevention (prophylaxis) of RDS in premature infants less than 29 weeks gestational age and at high risk for RDS
- Treatment (rescue) of premature infants less than or equal to 72 hours of age who develop RDS and require endotracheal intubation

Dosage

The recommended dose of calfactant is 3 mL/kg of body weight at birth. The dose should be delivered as two divided doses of 1.5 mL/kg. Each 3 or 6 mL of suspension contains enough preparation (105 or 210 mg of phospholipids) to treat a 1-kg or 2-kg infant. It is noted in the drug insert that calfactant prophylaxis should be administered as soon as possible, preferably no more than 30 minutes after birth.

Repeat doses, up to a total of three doses, can be given 12 hours apart. Repeat doses as early as 6 hours after the previous dose can be given if the infant is still intubated and requires 30% or greater oxygen for a partial pressure of arterial oxygen (PaO_2) of 80 mm Hg or less (manufacturer's literature).

Administration

Calfactant can be administered to an intubated infant either by side-port delivery or with a catheter. The preparation does not require reconstitution. Calfactant is an off-white suspension that requires gentle swirling or agitation, but not shaking, in the vial to ensure dispersion. Flecks may be visible in the suspension with foaming at the surface.

Side-Port Adapter. The dose is given in two aliquots of 1.5 mL/kg each. The infant should be positioned with either the right or the left side dependent for each aliquot. The suspension is instilled in small bursts timed to coincide with the inspiratory cycle, over 20 to 30 breaths. It is recommended that the infant be evaluated between repositioning for the second aliquot.

Catheter Administration. The dose is divided into four equal aliquots, with the catheter removed between each instillation and mechanical ventilatory support given for 0.5 to 2 minutes. Each aliquot is given with the infant in a different position (prone, supine, right lateral, and left lateral).

Poractant Alfa (Curosurf)

Poractant alfa (Curosurf) is a natural surfactant obtained as an extract of porcine lung. It is a suspension consisting of approximately 99% phospholipids (120 mg of phospholipids in the 1.5-mL vial and 240 mg of phospholipids in the 3-mL vial) and about 1% surfactant-associated proteins, including SP-B.

Indications for Use

Specific guidelines for use of poractant alfa (Curosurf) are as follows:

- For the treatment (rescue) of premature infants with RDS to reduce mortality and pneumothoraces

- Unlabeled uses: Severe MAS in term infants; respiratory failure caused by group B streptococcal infection in neonates

Dosage

The initial dose of poractant alfa is 2.5 mL/kg of birth weight. Subsequent doses of 1.25 mL/kg of birth weight can be given twice at 12-hour intervals if needed. The maximum recommended total dose (initial plus repeat doses) is 5 mL/kg.

Administration

Before use, the vial should be slowly warmed to room temperature. The vial should be turned upside down to disperse the suspension uniformly, without shaking. Poractant alfa does not need to be reconstituted. The dose is administered through a 5-F catheter positioned in the ETT, with the tip in the distal end of the ETT but not extended beyond the end of the ETT.

The dose is given in two aliquots. The infant is positioned with either the right or the left side down for the first aliquot. The catheter is then removed, and the infant is manually ventilated with 100% oxygen for 1 minute. When the infant is stable, the second aliquot is instilled with the alternate side down, after which the catheter is removed. Alternatively, the full dose may be given by using a dual lumen tube over 1 minute with the infant in the neutral position. Mechanical ventilation will not be interrupted. The airway should not be suctioned for 1 hour unless significant airway obstruction is evident not matter the administration method.

Lucinactant (Aerosurf)

Lucinactant (Aerosurf) is a synthetic peptide (KL4) containing surfactant replacement therapy that is aerosolized. In 2015, the suspension formula of lucinactant (Surfaxin) was removed from market to direct all funding to Aerosurf.

Hazards and Complications of Surfactant Therapy

CLINICAL CONNECTION

Possible hazards to the use of exogenous surfactants include airway occlusion, desaturation, bradycardia, overoxygenation and overventilation, apnea, and pulmonary hemorrhage.

Some complications in exogenous surfactant therapy are caused by the dosing procedure and others by the therapeutic effect of the drug itself. In the dosing procedure, relatively large volumes of suspension are instilled into neonatal-size airways, and this can block gas exchange, causing desaturation and bradycardia.

The effect of the drug in improving pulmonary compliance can lead to overventilation, excessive volume delivery from pressure-limited ventilation, and overoxygenation with dangerously high PaO_2 levels. As a result, the following complications or hazards can occur with surfactant therapy. In general, complications of prematurity may affect the response to exogenous surfactant.

Airway Occlusion, Desaturation, and Bradycardia

Because the current method of administration is by direct tracheal instillation, a large volume of surfactant suspension may cause an acute obstruction of infant airways, with subsequent hypoxemia

and bradycardia.¹⁹ Repetitive small additions of the dose and a transient increase in ventilating pressure may help distribute the surfactant to the periphery.

CLINICAL CONNECTION

If preoxygenation is done properly, changes are unlikely to occur, and if they do, they are brief. Bradycardia results more than likely from hypoxemia; however, it may be caused by vagal stimulation.

High Arterial Oxygen Values

A good response to exogenous surfactant results in better (higher) lung compliance, increased functional residual capacity (FRC), and concomitant improvement in oxygenation. Fractional inspired oxygen (FiO_2) settings must be lowered if PaO_2 improves, to prevent overoxygenation and the possibility of retinopathy of prematurity.

Overventilation and Hypocapnia

As lung compliance improves, peak ventilating pressure, expiratory baseline pressures, and ventilatory rate must be adjusted, or overventilation, leading to *hypocapnia* (low blood carbon dioxide) and pneumothorax, may occur.

CLINICAL CONNECTION

Compliance changes can occur quickly. The use of a flow-inflating bag allows the health care provider to more easily sense the direct change in compliance. This should result in changes by the practitioner to reduce ventilation pressure and rate, reducing overoxygenation and ventilation.

Apnea

Apnea has been noted to occur with intratracheal administration of surfactant.

Pulmonary Hemorrhage

Pulmonary hemorrhage seems to be the only consistent pulmonary complication associated with surfactant delivery. Pulmonary hemorrhage seems to be more frequent in infants who are younger, smaller, and with a patent ductus arteriosus (PDA). A causative link has not been found between pulmonary hemorrhage and PDA, and it has not been preventable.

Future Directions in Surfactant Therapy

KEY POINT

Exogenous surfactants are being investigated for clinical use in disease states such as acute respiratory distress syndrome (ARDS), meconium aspiration syndrome (MAS), and pneumonia.

In addition to RDS of the newborn, surfactant replacement therapy has been considered in treatment of MAS. In a meta-analysis, Soll and Dargaville²⁰ reported that surfactant therapy may be beneficial in reducing respiratory illness severity and reducing an infant's need for extracorporeal membrane oxygenation (ECMO).

Surfactant therapy had been studied for various adult respiratory disorders. This topic has been comprehensively reviewed by Hamm et al.⁵ ARDS in adults is a potential target for surfactant therapy. In RDS of the newborn, the primary abnormality of lung function is related to surfactant deficiency. In ARDS in adults, the surfactant deficiency is secondary to lung injury with complex inflammatory responses.⁵ This finding would suggest a difference in clinical response to surfactant therapy between premature infants and adults with ARDS. In addition, dose amount and administration techniques may need to be modified for therapy in adults, who have large lung volumes compared with infants. If lung injury in ARDS is nonuniform in distribution, exogenous surfactant, especially if aerosolized, may distribute unevenly to more compliant lung areas instead of distributing to areas needing surfactant the most.¹¹

The availability of newer surfactant preparations, specifically human recombinant surfactants, may offer better results to improve outcomes in adults with ARDS. Finer et al.²¹ found that lucinactant (Aerosurf) has been successful as an aerosol. The agent has been nebulized using a vibrating mesh for the possible treatment of ARDS in adults and neonates. Other adult respiratory disorders in which either surfactant replacement therapy or abnormal surfactant regulation may occur include pneumonia, lung transplants, sarcoidosis, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, alveolar proteinosis, obstructive lung disease (e.g., asthma), radiation pneumonitis, and drug-induced pulmonary disease.²²

RESPIRATORY CARE ASSESSMENT OF SURFACTANT THERAPY

Before Treatment

- Assess the need for surfactant therapy.

During Treatment and Short Term

- Monitor pulse and cardiac rhythm during and after administration.
- Monitor the infant for signs of airway occlusion (desaturation and bradycardia) during and after administration; if obstruction is evident, remove the infant from the ventilator and manually ventilate; in addition, saline lavage and aggressive suctioning to clear the airway may be needed.
- Monitor the skin color and activity level of the infant.
- Monitor chest rise for level of ventilation, or use electronic monitor, if available.
- Monitor arterial oxygen saturation, and adjust FiO_2 accordingly to prevent hyperoxia or hypoxia.
- Monitor transcutaneous PCO_2 , if possible, and be prepared to adjust level of ventilation, as needed, to prevent hypercarbia or hypocarbia.

Long Term

- Assess lung mechanics (exhaled volumes or peak inspiratory pressures) during mechanical ventilation to determine effectiveness of the exogenous agent in normalizing lung compliance. The instilled drug may cause changes within minutes in some cases.
- Assess the need for repeat dosing.

General Contraindications

- Consider possible hazards if pulse, cardiac rhythm, or arterial/transcutaneous blood gas values deteriorate.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

- What is the definition of a surface-active substance?
- In general, what is the clinical indication for use of exogenous surfactants?
- State the type (category) of exogenous surfactant for each of the following: beractant, calfactant, and poractant alfa.
- What are the major ingredients of natural pulmonary surfactant?
- Give the dosage schedule of each of the current exogenous surfactants.
- What is the difference between “rescue” treatment and “prophylaxis” with surfactants?
- Identify at least three possible adverse effects with the use of exogenous surfactant treatment.
- Why does the improvement in lung mechanics last after only one or two administrations of exogenous surfactant?
- How would you assess the effectiveness of exogenous surfactant treatment in a premature newborn with respiratory distress?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 16-year-old girl gave birth to a 25-week, 515-g girl by vaginal delivery. The mother had no prenatal care, and she had had premature rupture of the membranes 12 days before delivery. Immediately at birth, the newborn was intubated with a 2.5-mm oral ETT. Apgar scores after intubation and application of positive-pressure ventilation with a bag and mask were 7 and 9 at 1 minute and 5 minutes, respectively. After transfer to the neonatal intensive care unit, umbilical venous and arterial catheters were inserted, and the newborn was placed on mechanical ventilation with peak inspiratory pressure (PIP) of 20 centimeters of water (cm H₂O), positive end-expiratory pressure (PEEP) of 5 cm H₂O, respiratory rate (RR) of 60 breaths per minute (breaths/min), inspiratory time of 0.3 second, and FiO₂ of 1. Physical examination revealed pulse (P) of 140 beats/min, blood pressure (BP) of 34/22 mm Hg, temperature (T) of 99.6°F, and SpO₂ of 85% to 90%. Laboratory results revealed glucose at 39 mg/dL, white blood cell (WBC) count of 11,900/mm³, hematocrit of 47%, and platelets at 297,000/mm³. Chest radiograph showed stage II RDS.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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Corticosteroids in Respiratory Care

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Clinical Indications for Use of Inhaled Corticosteroids

Identification of Aerosolized Corticosteroids

Physiology of Corticosteroids

Identification and Source

Hypothalamic–Pituitary–Adrenal Axis

Hypothalamic–Pituitary–Adrenal Suppression With Steroid Use

Diurnal Steroid Cycle

Alternate-Day Steroid Therapy

Nature of Inflammatory Response

Inflammation in the Airway

Aerosolized Corticosteroids

Aerosolized Corticosteroid Agents

Beclomethasone Dipropionate (Qvar RediHaler)

Fluticasone Propionate (Flovent HFA, Flovent Diskus, and ArmonAir Respiclick/Digiclick)

Fluticasone Furoate (Arnuity Ellipta)

Budesonide (Pulmicort Flexhaler, Pulmicort Respules)

Mometasone Furoate (Asmanex Twisthaler, Asmanex HFA)

Ciclesonide (Alvesco)

Albuterol/Budesonide (AIRSUPRA)

Fluticasone Propionate/Salmeterol (AdvairDiskus, Advair HFA, Wixela Inhub AirDuo Respiclick/Digiclick)

Mometasone Furoate/Formoterol (Dulera)

Budesonide/Formoterol (Symbicort, Breyna)

Fluticasone Furoate/Vilanterol (Breo Ellipta)

Fluticasone Furoate/Umeclidinium/Vilanterol (Trelegy Ellipta)

Budesonide/Glycopyrrolate/Formoterol (Breztri Aerosphere)

Intranasal Corticosteroids

Pharmacology of Corticosteroids

Mechanism of Action

Effect on White Blood Cell Count

Effect on β Receptors

Hazards and Side Effects of Steroids

Systemic Administration of Steroids

Systemic Side Effects With Aerosol Administration

Topical (Local) Side Effects With Aerosol Administration

Oropharyngeal Fungal Infections

Dysphonia

Other Complications or Precautions

Clinical Application of Aerosol Steroids

Use in Asthma

Early Use of Corticosteroids in Asthma

Inhaled Corticosteroids for Acute Severe Asthma

Clinical Use of Inhaled Corticosteroids

Use in Chronic Obstructive Pulmonary Disease

Respiratory Care Assessment of Inhaled Corticosteroid Therapy

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to corticosteroids
2. Discuss the indications for inhaled corticosteroid use
3. List all available inhaled corticosteroids used in respiratory therapy
4. Differentiate among specific corticosteroid formulations
5. Describe the route of administration available for corticosteroids
6. Describe the mode of action for corticosteroids
7. Discuss the effect corticosteroids have on the white blood cell count
8. Discuss the effect corticosteroids have on β receptors
9. Differentiate between systemic and local side effects of corticosteroids
10. Discuss the use of corticosteroids in the treatment of asthma and chronic obstructive pulmonary disease
11. Be able to clinically assess corticosteroid use in patient care

KEY TERMS AND DEFINITIONS

Adrenal cortical hormones Chemicals secreted by the adrenal cortex, referred to as *steroids*.

Endogenous Refers to *inside*—produced by the body.

Exogenous Refers to *outside*—manufactured to be placed inside the body (e.g., medication).

Immunoglobulin E (IgE) Gamma globulin that is produced by cells in the respiratory tract.

Prostaglandins One of several hormone-type substances circulating throughout the body.

Steroid diabetes Hyperglycemia (i.e., increased plasma glucose levels) resulting from glucocorticoid therapy; glucocorticoids break down proteins and fats to generate building blocks for gluconeogenesis.

Steroids Also known as *glucocorticoids* or *corticosteroids*, agents that produce an antiinflammatory response in the body.

This chapter discusses the use of corticosteroids in respiratory care and provides a brief review of the physiology of endogenous corticosteroid hormones in the body. A brief description of inflammation, and specifically of airway inflammation in asthma, forms the basis for a discussion of the pharmacology of corticosteroids as antiinflammatory drugs. Aerosolized glucocorticoids and their uses and side effects are described.

Clinical Indications for Use of Inhaled Corticosteroids

Inhaled corticosteroids are available in formulations for oral inhalation (lung delivery) and intranasal delivery. Specific clinical applications are discussed more fully at the end of this chapter. General clinical indications for the use of inhaled corticosteroids are as follows:

- **Orally inhaled agents:** Maintenance and control therapy of chronic persistent asthma, identified as requiring step 2 care or greater.¹ *Step 2 asthma* is defined as asthma with symptoms occurring more than 2 days/week but not daily; night awakenings occurring 3 to 4 nights/month, with forced expiratory volume in 1 second (FEV₁) or peak expiratory flow (PEF) 80% of predicted or greater.
- Inhaled agents can be used with systemic corticosteroids in severe asthma and may allow for reduction or elimination of systemic corticosteroids for asthma control.
- Inhaled corticosteroids in combination with other agents are recommended by the American Thoracic Society (ATS)² and the Global Initiative for Chronic Obstructive Lung Disease (GOLD)³ for chronic obstructive pulmonary disease (COPD).
- **Intranasal aerosol agents:** Management of seasonal and perennial allergic and nonallergic rhinitis.

Identification of Aerosolized Corticosteroids

Increased numbers of aerosolized corticosteroid preparations are becoming available for oral inhalation and intranasal delivery. Table 11.1 lists currently available aerosol formulations of corticosteroids for oral inhalation, Table 11.2 lists combination corticosteroid agents for oral inhalation, and Table 11.3 lists intranasal formulations. The rationale for inhaled aerosol agents is discussed and the properties of corticosteroids required for success as topical agents are described subsequently, along with additional detail on individual agents.

Physiology of Corticosteroids

KEY POINT

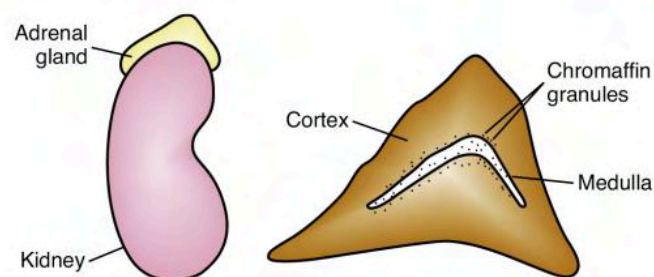
The *physiology* of *endogenous corticosteroids* involves a sequence of stimulation of the adrenal cortex through the *hypothalamic–pituitary–adrenal (HPA)* axis, in which increased blood levels of corticosteroid inhibit the HPA and adrenal cortex from further secretion.

Identification and Source

Corticosteroids are a group of chemicals secreted by the adrenal cortex and are referred to as **adrenal cortical hormones**. The adrenal or suprarenal gland is composed of two portions (Fig. 11.1). The inner zone is the adrenal medulla and produces epinephrine. The outer zone is the cortex, which is the source of corticosteroids. Three types of corticosteroid hormones are produced by the adrenal cortex: glucocorticoids (e.g., cortisol), mineralocorticoids (e.g., aldosterone), and sex hormones (e.g., androgens and estrogens). The mineralocorticoid aldosterone regulates body water by increasing the amount of sodium reabsorption in the renal tubules. The corticosteroids used in pulmonary disease are all analogs of cortisol or *hydrocortisone*, as it is also termed. Glucocorticoid agents are referred to as *glucocorticosteroids* and by the more general term *corticosteroid*, or simply as **steroids**.

KEY POINT

Corticosteroids secreted by the adrenal cortex include *glucocorticoids* (e.g., cortisol), *mineralocorticoids* (e.g., aldosterone), and *sex hormones* (e.g., androgen and estrogen).



• **Fig. 11.1** Location and cross section of adrenal, or suprarenal, gland. The outer portion, or cortex, of the adrenal gland is the source of corticosteroid hormones.

TABLE 11.1 Corticosteroids Available by Aerosol for Oral Inhalation*

Drug	Brand Name	Formulation and Dosage
Beclomethasone dipropionate HFA	Qvar RediHaler	<i>MDI</i> : 40 and 80 mcg/puff <i>Adults</i> ≥ 12 yr: 40, 80, 160, or 320 mcg twice daily <i>Children</i> ≥ 4 yr: 40–80 mcg bid
Fluticasone propionate	Flovent HFA	<i>MDI</i> : 44, 110, and 220 mcg/puff <i>Adults</i> ≥ 12 yr: 88 mcg bid, [†] 88–220 mcg bid, [‡] or 880 mcg bid [§] <i>Children</i> 4–11 yr: 88 mcg bid
	Flovent Diskus	<i>DPI</i> : 50, 100, and 250 mcg <i>Adults</i> : 100 mcg bid, [†] 100–250 mcg bid, [‡] 1000 mcg bid [§] <i>Children</i> 4–11 yr: 50–100 mcg bid
	Armonair/Digiclick	<i>DPI</i> : 55, 113, and 232 mcg/puff <i>Adults and children</i> ≥ 12 yr: 55–232 mcg bid
Fluticasone furoate	Arnuity Ellipta	<i>DPI</i> : 50, 100, and 200 mcg <i>Adults</i> ≥ 12 yr: 100 or 200 mcg once daily <i>Children</i> ≥ 5 yr: 50 mcg once daily
Budesonide	Pulmicort Flexhaler	<i>DPI</i> : 80 mcg/actuation and 160 mcg/actuation <i>Adults</i> : 160–320 mcg bid, ^{†‡} 360–720 mcg bid [§] <i>Children</i> ≥ 6 yr: 160–320 mcg bid
	Pulmicort Respules	<i>SVN</i> : 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL <i>Children</i> 1–8 yr: 0.5 mg total dose given once or twice daily in divided doses; ^{†‡} 1 mg given as 0.5 mg bid or once daily [§]
Mometasone furoate	Asmanex Twisthaler	<i>DPI</i> : 110 and 220 mcg/actuation <i>Adults and children</i> ≥ 12 yr: 220–880 mcg daily <i>Children</i> 4–11 yr: 110 mcg daily
	Asmanex HFA	<i>MDI</i> : 50, 100 and 200 mcg/actuation <i>Adults and children</i> ≥ 12 yr: 200–400 mcg bid <i>Children</i> 5–11 yr: 100 mcg bid
Ciclesonide	Alvesco	<i>MDI</i> : 80 and 160 mcg/actuation <i>Adults</i> ≥ 12 yr: 80–160 mcg twice daily, [†] or 80–320 mcg twice daily [‡]

*Individual agents are discussed in text. Detailed information about each agent should be obtained from the manufacturer's drug insert.
[†]Recommended starting dose if taking only bronchodilators.
[‡]Recommended starting dose if previously taking inhaled corticosteroids.
[§]Recommended starting dose if previously taking oral corticosteroids.
^{||}This dose should be used regardless of previous therapy.
bid, Twice daily; *DPI*, dry powder inhaler; *HFA*, hydrofluoroalkane; *MDI*, metered dose inhaler; *SVN*, small volume nebulizer.

CLINICAL CONNECTION

Glucocorticoids, often referred to simply as *steroids*, exert an *antiinflammatory effect* in the body.

Hypothalamic–Pituitary–Adrenal Axis

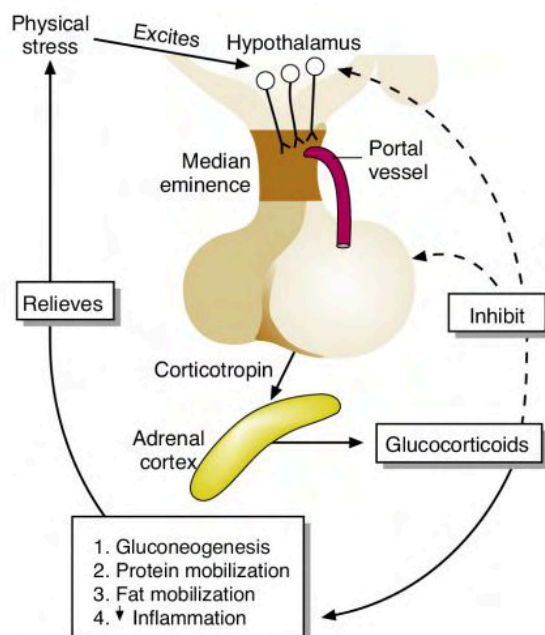
The side effects of corticosteroids and the rationale for aerosol or alternate-day therapy can be understood if the production and control of **endogenous** (the body's own) corticosteroids are grasped. The pathway for release and control of corticosteroids is the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 11.2). Stimulation of the hypothalamus causes impulses to be sent to the area known as the *median eminence*, where corticotropin-releasing

factor (CRF) is released. CRF circulates through the portal vessel to the anterior pituitary gland, which then releases corticotropin, or adrenocorticotrophic hormone (ACTH), into the bloodstream. ACTH, in turn, stimulates the adrenal cortex to secrete glucocorticoids, such as cortisol. Cortisol and glucocorticoids, in general, regulate the metabolism of carbohydrates, fats, and proteins, to increase levels of glucose for body energy. This is the reason cortisol and its analogs are called *glucocorticoids*. They can also cause lipolysis, redistribution of fat stores, and breakdown of tissue protein stores. These actions are the basis for many of the side effects seen with glucocorticoid drugs. The breakdown of proteins for use of the amino acids (gluconeogenesis) is responsible for muscle wasting, and the effects on glucose metabolism can increase plasma glucose levels. The latter is sometimes referred to as **steroid diabetes**.⁴

TABLE 11.2 Combination Corticosteroid Agents Available for Oral Inhalation*

Albuterol/formoterol	AIRSUPRA	<i>MDI</i> : 90 mcg albuterol/80 mcg budesonide <i>Adults 18 yr</i> : 2 inhalations as needed
Fluticasone propionate/ salmeterol	Advair Diskus	<i>DPI</i> : 100 mcg fluticasone/50 mcg salmeterol, 250 mcg fluticasone/50 mcg salmeterol, or 500 mcg fluticasone/50 mcg salmeterol <i>Adults and children ≥ 12 yr</i> : 100 mcg fluticasone/50 mcg salmeterol, 1 inhalation twice daily, about 12 hr apart (starting dose if not currently taking inhaled corticosteroids)
	Wixela Inhub	<i>DPI</i> : Maximal recommended dose is 500 mcg fluticasone/50 mcg salmeterol bid <i>Children ≥ 4 yr</i> : 100 mcg fluticasone/50 mcg salmeterol, 1 inhalation twice daily, about 12 hr apart (for patients who are symptomatic while taking inhaled corticosteroid)
	Advair HFA	<i>MDI</i> : 45 mcg fluticasone/21 mcg salmeterol, 115 mcg fluticasone/21 mcg salmeterol, or 230 mcg fluticasone/21 mcg salmeterol <i>Adults and children ≥ 12 yr</i> : 2 inhalations bid, about 12 hr apart
	AirDuo Respiclick/ Digihaler	<i>DPI</i> : 55 fluticasone/14 salmeterol, 113 fluticasone/14 salmeterol, or 232 mcg fluticasone/14 mcg salmeterol <i>Adults and children ≥ 12 yr</i> : Respiclick, any dose combination, 1 inhalation bid
Budesonide/formoterol fumarate HFA	Symbicort	<i>MDI</i> : 80 mcg budesonide/4.5 mcg formoterol and 160 mcg budesonide/4.5 mcg formoterol
	Breyna	<i>Adults and children ≥ 12 yr</i> : 160 mcg budesonide/9 mcg formoterol bid, 320 mcg budesonide/9 mcg formoterol bid; daily maximum: 640 mcg budesonide/18 mcg formoterol
Mometasone furoate/ formoterol fumarate HFA	Dulera	<i>MDI</i> : 50 mcg mometasone/5 mcg 100 mcg mometasone/5 mcg formoterol and 200 mcg mometasone/5 mcg formoterol
		<i>Adults and children ≥ 12 yr</i> : 2 inhalations of 100 mcg mometasone/5 mcg formoterol or 200 mcg mometasone/5 mcg formoterol, bid <i>Children 5–11 yr</i> : 2 inhalations of 50 mcg mometasone/5 mcg, bid
Fluticasone furoate/ vilanterol	Breo Ellipta	<i>DPI</i> : 100 mcg fluticasone/25 mcg vilanterol and 200 mcg fluticasone/25 mcg vilanterol <i>Adults</i> : 100 mcg fluticasone/25 mcg vilanterol daily and 200 mcg fluticasone/25 mcg vilanterol daily
Fluticasone furoate/ umeclidinium bromide/ vilanterol	Trelegy Ellipta	<i>DPI</i> : 100 mcg fluticasone/62.5 mcg umeclidinium/25 mcg vilanterol and 200 mcg fluticasone/62.5 mcg umeclidinium/25 mcg vilanterol <i>Adults</i> : 100 mcg fluticasone/62.5 mcg umeclidinium/25 mcg vilanterol daily and 200 mcg fluticasone/62.5 mcg umeclidinium/25 mcg vilanterol daily
Budesonide/glycopyrrolate/ formoterol	Breztri	<i>MDI</i> : 160 mcg budesonide/9 mcg glycopyrrolate /4.8 mcg formoterol
	Aerposphere	<i>Adults</i> : 160 mcg budesonide/9 mcg glycopyrrolate /4.8 mcg formoterol, 2 inhalations bid

*Individual agents are discussed in text. Detailed information about each agent should be obtained from the manufacturer's drug insert.
bid, Twice daily; *DPI*, dry powder inhaler; *HFA*, hydrofluoroalkane; *MDI*, metered dose inhaler.



• **Fig. 11.2** Hypothalamic–pituitary–adrenal axis regulation of corticosteroid secretion (see text for complete description of function).

Hypothalamic–Pituitary–Adrenal Suppression With Steroid Use

CLINICAL CONNECTION

Exogenous corticosteroid agents can suppress the hypothalamic–pituitary–adrenal (HPA) axis and the adrenal gland.

One of the most significant side effects of treatment with glucocorticoid drugs (**exogenous** corticosteroids) is adrenal suppression or, more generally, HPA axis suppression. When the body produces endogenous glucocorticoids, there is a normal feedback mechanism within the HPA axis to limit production. As glucocorticoid levels increase, release of CRF and ACTH is inhibited, and further adrenal production of glucocorticoids is stopped. This feedback inhibition of the hypothalamus and the pituitary is shown in Fig. 11.2 and is analogous to the servo mechanism, by which a thermostat regulates furnace production of heat by monitoring temperature levels.

The body cannot distinguish between its own endogenous glucocorticoids and exogenous glucocorticoid drugs. Administration of glucocorticoid drugs increases the body's level of these hormones, and this inhibits the hypothalamus and pituitary glands, which decreases adrenal production. This inhibition is

TABLE 11.3 Aerosol Corticosteroid Preparations Available for Intranasal Delivery*

Drug	Brand Name	Formulation and Dosage
Beclomethasone	Beconase AQ	<i>Spray:</i> 42 mcg/actuation <i>Adults ≥ 12 yr:</i> 1 or 2 sprays in each nostril bid <i>Children 6–11 yr:</i> 1 spray in each nostril bid, may increase to 2 sprays
	Qnasl	<i>Spray:</i> 80 mcg/actuation <i>Adults ≥ 12 yr:</i> 2 sprays in each nostril once daily
Triamcinolone acetonide	Nasacort Allergy 24 Hour [†]	<i>Spray:</i> 55 mcg/actuation <i>Adults and children ≥ 12 yr:</i> 2 sprays in each nostril once daily (starting dose). May reduce once symptoms improve. <i>Children 6–11 yr:</i> 1 spray in each nostril once daily (starting dose). May increase if symptoms do not improve. <i>Children 2–6 yr:</i> 1 spray in each nostril once daily
Flunisolide		<i>Spray:</i> 25 mcg/actuation and 29 mcg/actuation <i>Adults and children ≥ 14 yr:</i> 2 actuations in each nostril bid <i>Children 6–14 yr:</i> 1 actuation in each nostril tid or 2 actuations in each nostril bid
Budesonide	Rhinocort Rhinocort Allergy [†]	<i>Spray:</i> 32 mcg/actuation <i>Adults and children ≥ 6 yr:</i> 1 spray in each nostril daily (starting dose). Adults up to 4 sprays in each nostril daily. Children ≥ 6 yr: Up to 2 sprays in each nostril daily.
Fluticasone	Flonase Allergy Relief [†]	<i>Spray:</i> 50 mcg/actuation <i>Adults:</i> 2 sprays in each nostril once daily (starting dose) <i>Children ≥ 4 yr:</i> 1 spray in each nostril once daily (starting dose)
Mometasone furoate	Nasonex	<i>Spray:</i> 50 mcg/actuation <i>Adults and children ≥ 12 yr:</i> 2 sprays in each nostril once daily. Adults ≥ 18 may use 2 sprays in each nostril bid. <i>Children 2–11 yr:</i> 1 spray in each nostril once daily
Olopatadine hydrochloride/ mometasone furoate	Ryaltris	<i>Spray:</i> 665 mcg olopatadine/25 mcg mometasone/actuation <i>Adults and children ≥ 12 yr:</i> 2 sprays in each nostril bid.
Fluticasone furoate	Flonase Sensimist Allergy Relief [†]	<i>Spray:</i> 27.5 mcg/actuation <i>Adults and children ≥ 12 yr:</i> 2 sprays in each nostril once daily <i>Children 2–11 yr:</i> 1 spray in each nostril once daily
Ciclesonide	Omnaris	<i>Spray:</i> 50 mcg/actuation <i>Adults and children ≥ 6 yr:</i> 2 sprays in each nostril once daily
	Zetonna	<i>Spray:</i> 37 mcg/actuation <i>Adults and children ≥ 12 yr:</i> 1 spray in each nostril once daily

*Detailed information about each agent should be obtained from the manufacturer's drug insert.

[†]Only available over the counter.*bid*, Twice daily; *tid*, three times daily.

referred to as *HPA axis suppression* or, specifically, *adrenal suppression*. It is seen with systemic administration of corticosteroids, begins after 1 day of treatment, and is significant after 1 week of oral therapy at usual doses. A primary reason for using aerosolized glucocorticoids is to minimize adrenal, or HPA axis, suppression by minimizing the dosage and localizing the site of treatment.

If a patient has received oral corticosteroids and adrenal suppression has occurred, weaning from the exogenous corticosteroids through use of tapered dose therapy allows time for recovery of the body's own adrenal secretion. It should be noted that aerosolized corticosteroids do not deposit sufficient amounts of drug to replace the missing output of a suppressed adrenal gland. Therefore, a patient with adrenal suppression cannot be abruptly

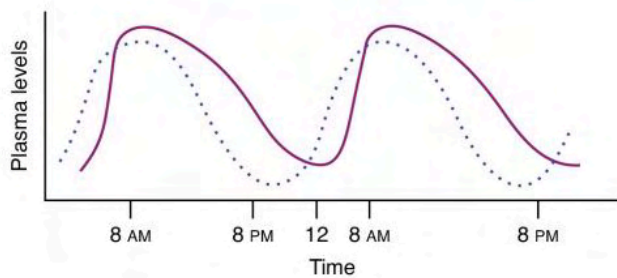
withdrawn from oral corticosteroids and placed on an aerosol dosage. The aerosol should be started while the oral agent is tapered off slowly at the same time.

Diurnal Steroid Cycle

KEY POINT

Levels of endogenous corticosteroids follow a daily, or *diurnal*, rhythm.

The production of the body's own glucocorticoids follows a rhythmic cycle, termed *diurnal* or *circadian rhythm*. This daily rise and fall of glucocorticoid levels in the body is shown in Fig. 11.3. On a daily schedule of daytime work and nighttime sleep, cortisol levels



• **Fig. 11.3** Diurnal variations in adrenocorticotropic hormone (dotted line) and cortisol (solid line) (see text for detailed description).

are highest in the morning around 8:00 AM. These high plasma levels inhibit further production and release of glucocorticoids and ACTH by the HPA axis because of the feedback mechanism previously described. During the day, plasma levels of ACTH (see Fig. 11.3, dotted line) and cortisol (see Fig. 11.3, solid line) gradually decrease. As the glucocorticoid level decreases, the anterior pituitary is reactivated to begin releasing ACTH, which stimulates production of cortisol by the adrenal cortex. This lag between increased ACTH and cortisol levels is illustrated in Fig. 11.3. One of the reasons for jet lag and the delay in adjusting to night shift from day shift is that this diurnal and regular rhythm of corticosteroid levels becomes out of synchronization with the time zone and the work time. Although a worker needs to sleep at 8:00 AM after working all night, the body is wide awake, with energy stores being released.

Alternate-Day Steroid Therapy

Alternate-day therapy mimics the natural diurnal rhythm by administration of a steroid drug early in the morning, when normal tissue levels are high. Suppression of the HPA system occurs at the same time it normally would with the body's own steroid, and on the alternate day the regular diurnal secretion in the HPA system can resume. Tissue side effects are minimized because the drug is administered at the time when tissues are normally exposed to elevated corticosteroid levels by the body's rhythm. Use of an intermediate-acting corticosteroid drug, with a duration of 12 to 36 hours, allows drug therapy to be restricted to alternate days.

Nature of Inflammatory Response

A major therapeutic effect seen with analogs of the natural (endogenous) adrenal cortical hormone hydrocortisone is an antiinflammatory action. Glucocorticoid analogs of endogenous hydrocortisone are used for this effect in treating asthma, which is an inflammatory process in the lungs. To understand the antiinflammatory activity of the glucocorticoid drugs used in asthma, the nature of inflammation in general and of airway inflammation, in particular, are reviewed briefly.

KEY POINT

Inflammation produces general symptoms of redness, swelling, heat, and pain.

A general definition of *inflammation* is the response of vascularized tissue to injury. An excellent and still applicable description of inflammation was given in the first century AD by Celsus: “*rubor et tumor cum calore et dolore*,” which is translated as “redness and swelling with heat and pain.” This is the most general description of an inflammatory reaction to injury, such as a cut, wound infection, splinter, burn, scrape, or bee sting.

An update of Celsus' description occurred in the 1920s with Lewis' characterization known as the *triple response*:

1. **Redness:** Local dilation of blood vessels, occurring in seconds
2. **Flare:** Reddish coloration several centimeters from the site, occurring 15 to 30 seconds after injury
3. **Wheal:** Local swelling, occurring in minutes

The process of inflammation producing the visible results described by Celsus, Lewis, and others is caused by the following four major categories of activity:

1. **Increased vascular permeability:** An exudate is formed in the surrounding tissues.
2. **Leukocytic infiltration:** White blood cells (WBCs) emigrate through capillary walls (diapedesis) in response to attractant chemicals (chemotaxis).
3. **Phagocytosis:** WBCs and macrophages (in the lungs) ingest and process foreign material, such as bacteria.
4. **Mediator cascade:** Histamine and chemoattractant factors are released at the site of injury, and various inflammatory mediators, such as complement and arachidonic acid products, are generated.

Inflammation in the Airway

KEY POINT

In the airway, inflammation is mediated by various cells, such as *eosinophils*, *basophils*, *macrophages*, *mast cells*, *T lymphocytes*, and *epithelial or endothelial cells*, in response to the release of *mediators of inflammation*. This process is complex and involves several mediators, including the *arachidonic acid cascade* (**prostaglandins** and leukotrienes); *histamine*; and various *cytokines*, such as interleukins. These mediators further amplify the inflammatory response by attracting the cells mentioned previously to the airway and inducing the release of *adhesion* factors (e.g., intercellular adhesion molecule [ICAM]) to bind inflammatory cells to the airway surface.

Inflammation can occur in the lungs in response to various causes, including direct trauma (gunshot wound, stabbing), indirect trauma (blunt injury to the chest), inhalation of noxious or toxic substances (chlorine gas, smoke), respiratory infections and systemic infections producing septicemia and septic shock in acute respiratory distress syndrome (ARDS), and allergenic or nonallergenic stimulation in asthma. The two most common inflammatory diseases of the airway seen in respiratory care are chronic bronchitis, which is usually caused by tobacco smoking, and asthma, which can be caused by a range of triggers and involves a complex pathophysiology.

Because glucocorticoids are a mainstay for treating asthma, the multiple pathways and mediators for the genesis of airway inflammation seen in asthma are briefly described. Asthma is currently understood as a disease in which there is chronic inflammation of the airway wall, causing airflow limitation and a hyperresponsiveness to various stimuli^{4,5} (Box 11.1). The airway inflammation is mediated by inflammatory cells, such as mast cells, eosinophils, T lymphocytes, and macrophages. The mast cell and the eosinophil are considered to be the major effector cells of the inflammatory response, regardless of whether the asthma is of the allergic or nonallergic type.⁶ T lymphocytes may be pivotal in coordinating the inflammatory response by releasing numerous proinflammatory cytokines (proteins that regulate immune and inflammatory responses), which act on basophils, epithelial cells, and endothelial cells in the airway to further the inflammatory process. The potent mediators released during an asthmatic reaction cause airway smooth muscle contraction (bronchospasm), increased

• BOX 11.1 Operational Definition of Asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to various stimuli.

National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, National Institutes of Health. (2007). *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*, NIH Publication No. 08-4051, Bethesda, Maryland; National Institutes of Health.

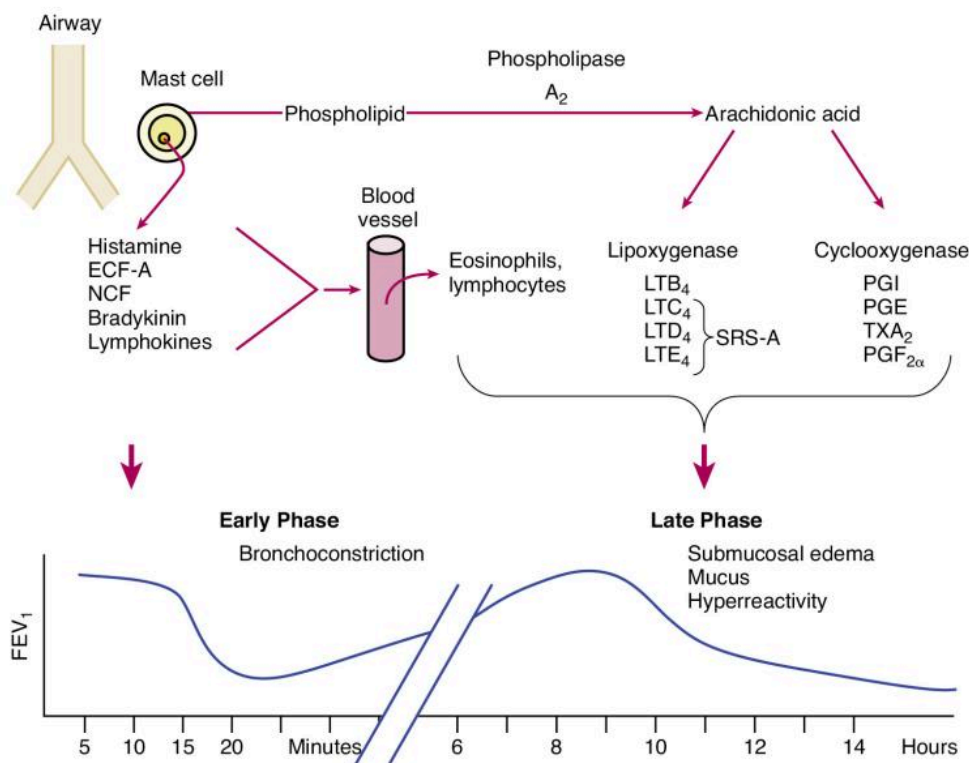
microvascular leakage and airway wall swelling, mucus secretion, and remodeling of the airway wall over the longer term. In an acute state, people with asthma exhibit wheezing, breathlessness, chest tightness, and cough, especially at night or early morning. The acute symptoms produced by the airway inflammation are at least partly reversible either spontaneously or with pharmacologic treatment. Treatment with antiinflammatory agents, such as glucocorticoids, is important to reduce the basal level of airway inflammation, airway hyperresponsiveness, and the predisposition to acute episodes of obstruction.

Asthmatic reactions are biphasic, with an early phase and a late phase. Fig. 11.4 shows a conceptual representation of the overall process. After an insult to the asthmatic airway by an allergen, cold air, viral infection, or noxious gas, there is evidence that the

early asthmatic response is caused by **immunoglobulin E (IgE)**-dependent activation of airway mast cells, which can release inflammatory mediators, such as histamine, prostaglandin D_2 (PGD_2), and leukotriene C_4 .⁵ The immediate response of the airway to chemicals, such as histamine, is bronchospasm. This response peaks at about 15 minutes and then declines over the next hour; this produces the early phase decrease in expiratory flow rates illustrated in Fig. 11.4.

Although early bronchoconstriction of smooth muscle may be self-limiting or respond to β agonists, cellular events can continue to progress. Mast cell mediators and the release of cytokines recruit other inflammatory cells (eosinophils, basophils, monocytes/macrophages, and lymphocytes) by activating epithelial cells and endothelial cells to release adhesion molecules (e.g., ICAM) and other cytokines to cause the late-phase reaction. During the late-phase response, mast cells and recruited eosinophils, lymphocytes, or macrophages that have infiltrated the airway release a range of inflammatory mediators. Neutrophils are not generally associated with asthma and allergic reactions in the absence of infection. The late asthmatic response occurs 6 to 8 hours after a challenge, and it may last for 24 hours. The late-phase reaction is thought to be reflective of the chronic inflammation characterizing asthma between acute episodes.⁶

Phospholipids in the cell membrane of mast cells and other cells are converted by phospholipase A_2 (PLA_2) to arachidonic acid and then to various bronchoactive and vasoactive substances by the two metabolic paths shown in Fig. 11.4: the cyclooxygenase and lipoxygenase pathways. The term *eicosanoid* is used to refer to the products of the two pathways. The migration of eosinophils and lymphocytes and further development of inflammation-producing



• **Fig. 11.4** Conceptual illustration of inflammatory asthmatic response in the airway, producing a biphasic deterioration in expiratory flow rates as described as an early-phase and late-phase response to triggering stimuli. *ECF-A*, Eosinophilic chemotactic factor; *FEV₁*, forced expiratory volume in 1 second; *LTB₄*, leukotriene B_4 ; *LTC₄*, leukotriene C_4 ; *LTD₄*, leukotriene D_4 ; *LTE₄*, leukotriene E_4 ; *NCF*, neutrophil chemotactic factor; *PGE*, prostaglandin E ; *PGF_{2α}*, prostaglandin $F_{2α}$; *PGI*, prostaglandin I ; *SRS-A*, slow-reacting substance of anaphylaxis; *TXA₂*, thromboxane A_2 .

chemicals, such as the arachidonic acid metabolites and cytokines, all contribute to build an inflammatory response in the lung.⁷ In addition to smooth muscle spasm, mucus secretion occurs, along with mucosal swelling resulting from increased vascular permeability. Shedding of airway cells (*desquamation*) and goblet cell hyperplasia are seen. The result is mucous plugging of the airway, complicated by the cellular debris in the bronchial lumen. The pathology of bronchial asthma has been described as “chronic desquamating eosinophilic bronchitis.”⁸ These airway changes lead to further bronchial hyperreactivity seen in asthma. There is evidence of airway remodeling, with increased tenascin (an extracellular matrix protein for cell development), collagens, and fibronectin, all of which can cause thickening of the basement membrane in the airway wall. This airway remodeling deregulates communication between cells, promoting epithelial damage and enhancing the inflammatory response.⁹

Aerosolized Corticosteroids

Several corticosteroid preparations, such as hydrocortisone, cortisone, prednisone, prednisolone, and methylprednisolone, are available, and all have antiinflammatory activity. However, these agents produce undesirable systemic side effects when used to treat asthma, COPD, and inflammation of the lung. As with all inhaled agents, topical application of corticosteroids is intended to provide direct application of the drug to the lung or nasal passages and reduce systemic side effects.

Aerosolized Corticosteroid Agents

CLINICAL CONNECTION

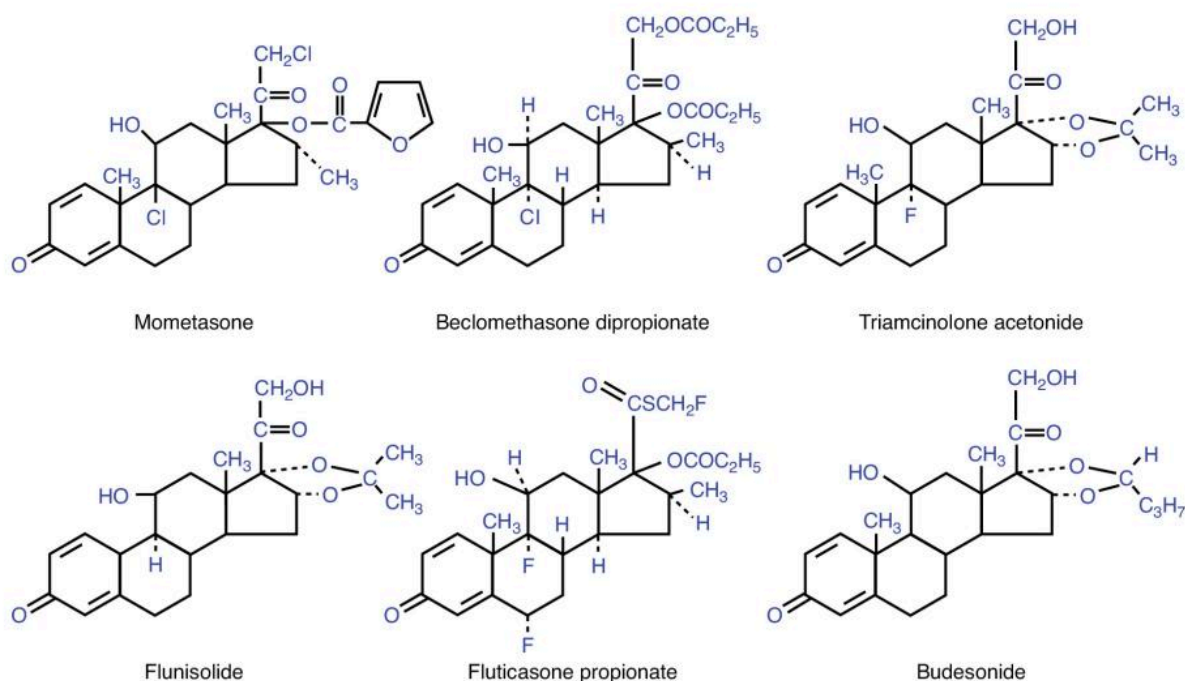
The use of aerosolized corticosteroids targets inflammation in the airway, with a smaller dose reducing systemic side effects.

Several aerosol steroid agents, all of which are glucocorticoids, are available for inhalational use in the United States at the time of this edition. These are listed in Table 11.1, which summarizes steroids used for oral inhalation; corticosteroids in combination with other agents are listed in Table 11.2, and Table 11.3 lists agents for intranasal delivery, with their strengths and recommended doses. Originally, in the United States, all of the orally inhaled corticosteroids were available as metered dose inhaler (MDI) formulations. However, dry powder inhalers (DPIs)—Diskus (fluticasone), Arnuity Ellipta (fluticasone), Pulmicort Flexhaler (budesonide), and Asmanex Twisthaler (mometasone furoate)—have also been introduced, along with the only approved small volume nebulizer (SVN) formulation (budesonide [Pulmicort Respules]). At the time of this edition, all the MDI formulations are available with hydrofluoroalkane (HFA) propellant (beclomethasone, fluticasone, mometasone, and ciclesonide).

These agents possess a high topical-to-systemic potency ratio, which makes them suitable for control of asthma or COPD with minimal systemic side effects. The chemical structures of the aerosol agents available for oral and nasal inhalation are shown in Fig. 11.5. Each of the aerosol agents is briefly described next.

Beclomethasone Dipropionate (Qvar RediHaler)

Beclomethasone dipropionate (Qvar RediHaler) has been known by several names, including Vanceril and Beclovent; however, with the transition from chlorofluorocarbon (CFC)-propelled MDI formulations, beclomethasone dipropionate has been reformulated with an HFA propellant in a 40- and 80-mcg MDI strength as Qvar (see Table 11.1). Qvar RediHaler is now available as a breath-actuated MDI. The design has primeless canister that does not need to be shaken, and thus priming is not required. Because of the breath-actuated design, a spacer or valved holding chamber should be used. The patient will need a minimum of 20 L/min to activate a dose. Lung deposition with Qvar has been measured at 50% to 60% of the emitted dose (see discussion of MDIs in



• **Fig. 11.5** Structures of aerosolized corticosteroids, showing the common steroid nucleus, and modifications to enhance topical antiinflammatory action.

Chapter 3). The usual starting dose of Qvar is 40 to 80 mcg twice daily (see Table 11.1).

An aerosol dose of 400 mcg is approximately equivalent to 5 to 10 mg of oral prednisone. When inhaled by aerosol, the swallowed drug is slowly absorbed from the gastrointestinal tract, and most of what is absorbed is quickly (half-life in the liver is 10 minutes) broken down in its first passage through the liver, preventing high plasma levels.

Absorption of the drug across the pulmonary epithelium is good, but rapid inactivation prevents systemic accumulation. After inhalation of a 2-mg dose, plasma levels of beclomethasone dipropionate are very low, but the active metabolite, beclomethasone monopropionate (often designated 17-BMP), reaches significant plasma levels of 1.8 to 2.5 ng/mL.¹⁰

Fluticasone Propionate (Flovent HFA, Flovent Diskus, and ArmonAir Respiclick/Digiclick)

Fluticasone propionate (Flovent HFA, Flovent Diskus, and ArmonAir Respiclick/Digiclick) is a synthetic, trifluorinated glucocorticoid with high topical antiinflammatory potency and is available in MDI and DPI forms. The MDI is available in three different strengths: 44, 110, and 220 mcg. Fluticasone propionate is available as a generic MDI. DPI Respiclick/Digiclick is also available in three different strengths: 50, 100, and 250 mcg and 55, 113, and 2232 mcg, respectively. ArmonAir Respiclick/Digiclick is a DPI and a spacer should not be used with it, even though it may look like an MDI. The drug is a further analog of previous agents with high topical potency, synthesized to avoid systemic side effects. Fluticasone is derived from the 17 β -carbothioate series of androstane analogs, a group that has very weak HPA axis inhibitory activity but high antiinflammatory effect.¹¹ Using flucinolone acetate as a reference standard, fluticasone propionate was found to have an antiinflammatory potency of 91 in mice,¹² with an HPA axis inhibitory activity of only 1, giving a therapeutic index (antiinflammatory potency/HPA axis potency) of 91. By comparison, beclomethasone dipropionate has an antiinflammatory potency of 21, with an HPA axis inhibitory potency of 49 in mice.¹³ If given by subcutaneous injection to mice, fluticasone propionate exhibits HPA inhibition; however, the oral route gives only weak HPA axis suppression; this is useful with inhaled aerosols because a portion of the aerosol may be swallowed and contribute to systemic activity of a drug. An explanation for the weak HPA axis suppression when given orally may be its high first-pass effect, resulting in less than 1% of active drug dose in the circulation because fluticasone is rapidly metabolized in the liver into the inactive product 17 β -carboxylic acid.¹²

Fluticasone Furoate (Arnuity Ellipta)

Fluticasone furoate (Arnuity Ellipta) is available as a DPI delivering 100 and 200 mcg/inhalation for once-daily maintenance treatment of asthma in patients aged 12 years and older. Fluticasone furoate and fluticasone propionate differ in that they are different salts or esters from different acids. The difference appears to be that the furoate salt has better affinity for the glucocorticoid receptor, thus providing a longer duration of action. Because of this affinity, fluticasone furoate lends itself to once daily dosing. Inspiratory flow of patients will determine the dose of each inhalation. An inspiratory flow of 60 L/min will provide at least 90% of the dose.

Budesonide (Pulmicort Flexhaler, Pulmicort Respules)

Budesonide (Pulmicort, Pulmicort Respules) is available as a DPI (Pulmicort Flexhaler) or as an inhalation solution (Pulmicort

Respules). The DPI delivers two strengths 80 and 160 mcg/metered dose—and Pulmicort Respules is available in doses of 0.25, 0.5, and 1 mg. The benefit of using Respules is that it can be mixed with other agents, such as bronchodilators (e.g., albuterol, levalbuterol, and ipratropium). Numerous studies have shown that mixing the agents had no effect on the drugs mixed.¹³

Budesonide is a topically active inhaled corticosteroid with a potency greater than that of beclomethasone dipropionate, triamcinolone, or flunisolide, but it is less potent than fluticasone, as estimated by skin vasoconstriction assay. With oral administration, only 10% of budesonide enters the systemic circulation because of high (approximately 89%) first-pass metabolism in the liver. After inhalation with a spacer device, peak plasma concentrations occur between 15 and 45 minutes. The plasma half-life is 2 hours. There appears to be minimal metabolism in the lung, with approximately 70% of the inhaled dose reaching the circulation.¹⁴ Budesonide was found to exhibit about half the adrenal suppression of fluticasone on a microgram equivalent basis in patients with asthma.¹⁵

Mometasone Furoate (Asmanex Twisthaler, Asmanex HFA)

Mometasone furoate is available as a MDI and DPI. McCormack and Plosker¹⁶ reviewed its use in asthma. Asmanex can be given once or twice daily. Single-day dosing may be beneficial to increase consistency in the usage of an inhaled corticosteroid. Karpel et al.¹⁷ found that pulmonary function results increased in patients receiving once-daily Asmanex compared with placebo in patients previously using twice-daily doses of inhaled corticosteroids. Asmanex is approved for patients as young as 4 years of age.

Ciclesonide (Alvesco)

Ciclesonide (Alvesco) is a prodrug; once it enters the body, it is enzymatically converted to des-ciclesonide. Ciclesonide has been shown to decrease the incidence of *Candida albicans* infection in the mouth. Although it is listed to be dispensed twice daily, the literature describes once-daily dosing to be as effective as twice-daily dosing with other inhaled corticosteroids. Des-ciclesonide has a 120 times greater affinity for the glucocorticoid receptor. Ciclesonide is approved by the US Food and Drug Administration (FDA) only for individuals older than 12 years; however, several pediatric studies exist, which may offer potential to prescribe off-label.

Albuterol/Budesonide (AIRSUPRA)

Albuterol/budesonide (AIRSUPRA) is a combination agent for PRN treatment of asthma in patients 18 years and older. This combination of a short-acting β_2 -agonist and a corticosteroid is only used as a rescue inhaler to treat bronchospasms. The agents are dispensed as an MDI. The dosage and availability of these agents and others can be found in Table 11.2.

Fluticasone Propionate/Salmeterol (Advair Diskus, Advair HFA, Wixela Inhub AirDuo Respiclick/Digiclick)

Fluticasone propionate/salmeterol (Advair Diskus, Advair HFA, Wixela Inhub, AirDuo Respiclick/Digiclick) is a combination product of the corticosteroid fluticasone with the long-acting β_2 -agonist bronchodilator salmeterol. Fluticasone propionate/salmeterol is available as a generic DPI, similar to the respiclick. The Respiclick/Digiclick, a DPI, looks similar to a MDI but should not be used with a spacer or valved holding chamber. The combination of inhaled steroid and long-acting β_2 -agonist

in a convenient dose package is useful in patients with asthma requiring the need for both types of drug. In a large multicenter clinical study by Shapiro et al.,¹⁸ patients with asthma who were taking medium doses of inhaled corticosteroids were treated with 250 mcg of fluticasone in combination with 50 mcg of salmeterol from the DPI Diskus device for 12 weeks. Patients in the treatment group had significantly better FEV₁ profiles over 12 hours, a significantly greater probability of remaining in the study and not withdrawing because of worsening symptoms, a significantly increased morning PEF, reduced asthma symptom scores, reduced rescue albuterol use, and significantly fewer nights with no awakenings compared with patients taking salmeterol or fluticasone alone or a placebo.

Mometasone Furoate/Formoterol (Dulera)

Mometasone furoate/formoterol (Dulera) is a combination product of the corticosteroid mometasone with the long-acting β_2 -agonist bronchodilator formoterol (see Chapter 6 for a discussion of formoterol). Dulera is available as an MDI in three strengths (mometasone/formoterol): 50 mcg/5 mcg, 100 mcg/5 mcg, and 200 mcg/5 mcg. In two randomized, double-blind, placebo-controlled studies involving more than 1500 patients, Dulera was able to increase lung function as a combination drug better than formoterol alone or a placebo. Fewer patients reported a deterioration on Dulera than formoterol alone (manufacturer's literature).

Budesonide/Formoterol (Symbicort, Breyna)

Budesonide/formoterol (Symbicort, Breyna) is a combination product of the corticosteroid budesonide with the long-acting β_2 -agonist bronchodilator formoterol (see Chapter 6 for a discussion of formoterol). Symbicort is available as an MDI in two strengths (budesonide/formoterol): 80 mcg/4.5 mcg and 160 mcg/4.5 mcg. In two large, double-blind, placebo-controlled studies involving more than 100 patients, Symbicort was able to increase lung function as a combination drug better than either drug separately or a placebo, and it was found that the combination therapy was able to increase lung function 15 minutes after administration (manufacturer's literature). In March 2022, Mylan received FDA approval to offer Symbicort as a generic, known as Breyna.

Although combination products have the disadvantage of not allowing changes in dose for each drug separately and this use has been discouraged, there is evidence of a beneficial, complementary interaction between glucocorticoids and β -adrenergic agonists. The addition of long-acting bronchodilators to inhaled corticosteroids has no negative effect and shows improvements in lung function and symptom control, as shown in the clinical trial by Shapiro et al.,¹⁸ by Chung¹⁹ for Advair, and by Jenkins et al.²⁰ for Symbicort.

The interaction results from the following known or investigational actions of steroids and β agonists:

- Steroids increase β_2 -adrenergic receptor transcription (upregulation of β receptors).^{19,21}
- Inhaled corticosteroid therapy can provide partial protection against the development of tolerance to β_2 -adrenergic agonists.¹⁹
- Salmeterol has been shown to promote binding of the glucocorticoid receptor to the response element of the cell's nuclear DNA, *without the glucocorticoid present*, in vascular cells, initiating the antiinflammatory effect at least partially.²¹

If management of asthma requires a long-acting β agonist and an inhaled corticosteroid, the combination products fluticasone

propionate/salmeterol and budesonide/formoterol offer the advantage of more convenient, single-formulation dosing. GINA² and the Expert Panel⁴ on Asthma have found the use of budesonide/formoterol as a preferred agent in maintenance, but also in adults as a rescue agent.

Fluticasone Furoate/Vilanterol (Breo Ellipta)

Breo Ellipta is a combination product of the corticosteroid fluticasone furoate with the long-acting β_2 -agonist bronchodilator vilanterol (see Chapter 6 for a discussion of vilanterol). Breo Ellipta is a DPI containing two double-foil blister strips of powder formulation for oral inhalation. One strip contains 100 or 200 mcg of fluticasone furoate per blister, and the other contains 25 mcg of vilanterol per blister. The combination product is approved for once-daily treatment of COPD and for patients with asthma who are 18 years old or older.

CLINICAL CONNECTION

Trelegy Ellipta and Breztri Aerosphere are fixed-drug combinations that include three different agents into one inhaler. This is termed "triple therapy" in the maintenance of chronic obstructive pulmonary disease (COPD) and asthma.

Fluticasone Furoate/Umeclidinium/Vilanterol (Trelegy Ellipta)

Trelegy Ellipta is a fixed-drug combination on the market and termed "triple therapy" because it is the first to incorporate at three agents used to treat COPD in one inhaler. The DPI provides 100 mcg fluticasone furoate, 62.5 mcg umeclidinium bromide, and 25 mcg of vilanterol per blister, respectively. This agent is used in the maintenance treatment of COPD. Late in 2020, Trelegy was provided an indication to treat asthma in patients 18 years and older. In a systematic review²² it was noted that triple therapy assisted in reducing asthma exacerbations and overall asthma control in adults and children as young as 6 years of age.

Budesonide/Glycopyrrolate/Formoterol (Breztri Aerosphere)

Breztri Aerosphere is the newest fixed-drug combination with three agents, known as "triple therapy." The combination of agents utilizes a pressurized MDI and is indicated in the maintenance treatment of COPD. The MDI delivers 160 mcg of budesonide, 9 mcg of glycopyrrolate, and 4.8 mcg of formoterol per actuation. Heo²³ reviewed Breztri to other triple therapies and found no difference in treatment of COPD.

Intranasal Corticosteroids

All the steroids available are orally inhaled agents, and many are also available in an intranasal formulation. Exact indications for the intranasal preparations vary by specific agent, but intranasal steroids generally are used to treat allergic or inflammatory nasal conditions and seasonal or perennial allergic or nonallergic rhinitis and to prevent recurrence of nasal polyps. Available preparations are listed in Table 11.3, with strengths and recommended doses. Other agents that are used to treat seasonal allergic rhinitis include H₁-receptor antagonists (e.g., loratadine), cromolyn sodium (see Chapter 12), topical vasoconstrictors, such as oxymetazoline or ephedrine, and anticholinergics, such as ipratropium bromide.

KEY POINT

Aerosolized glucocorticoids all are topically active drugs and include beclomethasone dipropionate, triamcinolone acetonide, flunisolide, budesonide, fluticasone propionate, fluticasone furoate, and mometasone furoate. Aerosol agents are available for *oral inhalation* in the control of asthma and chronic obstructive pulmonary disease (COPD) and *intranasal* administration for rhinitis.

Pharmacology of Corticosteroids

KEY POINT

Glucocorticoids are lipid soluble and act on intracellular receptors to produce antiinflammatory effects.

The inflammatory process can be reduced or blocked by the antiinflammatory effects of glucocorticoids. The beneficial effect of glucocorticoids in asthma and other inflammatory diseases results from their ability to inhibit the activity of inflammatory cells and mediators of inflammation.

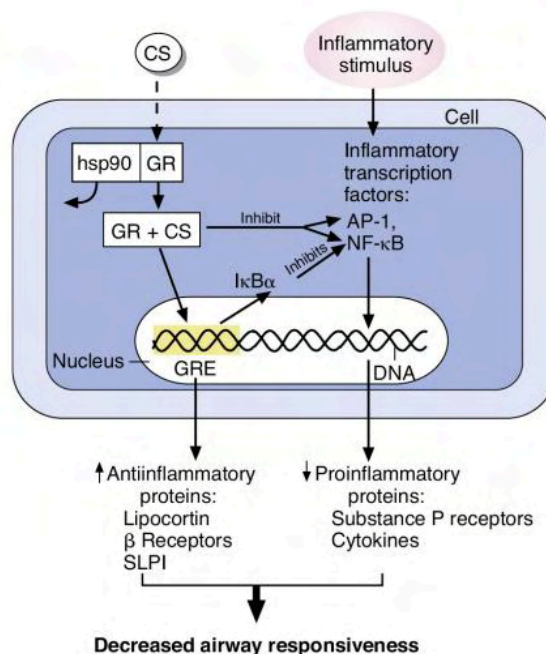
Mechanism of Action

KEY POINT

The mechanism of action of glucocorticoids is through the *upregulation* of antiinflammatory proteins (e.g., β receptors and lipocortin) and the *down-regulation* of proinflammatory proteins (e.g., cytokines and substance P).

Glucocorticoids are highly lipophilic and enter airway cells to bind to intracellular receptors.²⁴ This mechanism of drug signaling action was described briefly in [Chapter 2](#) in the discussion of the pharmacodynamics of lipid-soluble drugs that interact with intracellular receptors. Originally, investigators thought that corticosteroids or, more simply, steroids exerted antiinflammatory activity by stabilizing lysosomes within neutrophils; this prevented degranulation and an inflammatory response. In the mid-1960s, steroid receptors were discovered, and it was realized that steroids modify the inflammatory response by inducing gene expression within the cell. By the 1980s, it was shown that glucocorticoids induce gene expression for the antiinflammatory protein lipocortin, which inhibits the enzyme PLA_2 , preventing the arachidonic acid cascade, which leads to prostaglandin synthesis and lipoxigenase products.⁶ However, now it is understood that PLA_2 inhibition is only one of multiple mechanisms by which steroids attenuate the inflammatory response.^{25–27}

Steroids suppress a local or systemic inflammatory response by at least three general actions; these actions are illustrated in [Fig. 11.6](#). Generally, steroids diffuse into the cell and bind to a glucocorticoid receptor. Before binding by a steroid, the glucocorticoid receptor is in an inactive state and is bound to a protein complex termed *heat shock protein 90* (*hsp90*), which prevents the unoccupied receptor from translocating to the nucleus of the cell. When the steroid binds to the receptor, *hsp90* dissociates, and the steroid–receptor complex translocates to the cell nucleus. One general action (not always the first temporally) of a glucocorticoid is to upregulate the transcription of antiinflammatory genes for substances, such as lipocortin, as previously described.^{25–27} In the nucleus, the steroid produces this part of its effect on the cell by binding to portions of the nuclear DNA termed *glucocorticoid response elements*. Binding of the drug–receptor complex to



• **Fig. 11.6** Proposed mechanism of action by which glucocorticoids exert an antiinflammatory effect. AP-1, Activator protein-1; CS, corticosteroid; DNA, deoxyribonucleic acid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; *hsp90*, heat shock protein 90; $I\kappa B\alpha$, inhibitor of nuclear factor- κB ; NF- κB , nuclear factor- κB ; SLPI, secretory leukocyte protease inhibitor.

glucocorticoid response elements upregulates, or induces, transcription of antiinflammatory substances, such as lipocortin, neutral endopeptidase, secretory leukocyte protease inhibitor (sLPI), or inhibitors of plasminogen activator.⁶ These are all antiinflammatory substances. A second general action of glucocorticoids is the suppression of factors such as activator protein-1 (AP-1) and nuclear factor- κB (NF- κB), which cause transcription of genes involved in inflammation. This suppression may be by means of a direct interaction with these transcription factors, by which the transcription factor is inactivated before it induces gene expression in the nucleus.²⁵ Direct inactivation of AP-1 and NF- κB leads to downregulation of gene expression for proinflammatory mediators, such as cytokines. NF- κB regulates genes that have increased expression in asthma, including genes for cytokines, such as interleukins (e.g., interleukin-1 [IL-1] and interleukin-3 [IL-3]); chemokines; tumor necrosis factor- α (TNF- α); nitric oxide synthase, which produces nitric oxide in the airway; and adhesion molecules, which promote recruitment and attachment of leukocytes (eosinophils and basophils) from the circulation to the airway endothelium.^{14,25,26} A direct inactivation of inflammatory transcription factors, such as AP-1 or NF- κB , may account for the rapidity with which some cellular effects of steroids are seen and that are not well explained by the time needed for modification of gene expression within a cell. A third action of glucocorticoids is to upregulate the expression of inhibitors of NF- κB , such as the inhibitor of nuclear factor protein ($I\kappa B\alpha$). This inhibitor of NF- κB further suppresses gene expression for proinflammatory proteins, such as cytokines.^{26–28}

The general result of these actions is to *induce* gene expression for antiinflammatory proteins and receptors and to *suppress* gene expression for proinflammatory proteins. Overall, glucocorticoids inhibit the cytokine production responsible for recruitment and

• BOX 11.2 Cytokines* Involved in Airway Inflammation That Are Suppressed by Glucocorticoids

Tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1)	Are released from macrophages, monocytes, and other cells to activate endothelial cells to recruit neutrophils, eosinophils, and basophils from circulation
IL-4 IL-13	Are released from lymphocytes and basophils and associated with allergic diseases; cause endothelium to bind basophils, eosinophils, monocytes, and lymphocytes
IL-3, IL-5, granulocyte macrophage-colony-stimulating factor (GM-CSF), interferon- γ (IFN- γ)	Cause eosinophil priming, resulting in prolonged eosinophil survival and potentiated degranulation to release inflammatory substances
Chemokines	Family of small cytokines (molecules with masses of 8–10 kDa) having many chemotactic properties to attract cells to a site. <i>Example:</i> Regulated on activation, normal T-cell expressed and secreted (RANTES), one of the most potent chemokines, which induces eosinophil and lymphocyte migration and attraction

*Cytokines are proteins secreted by various cells, such as lymphocytes, that regulate local and systemic inflammatory responses.

migration of inflammatory cells, such as eosinophils and lymphocytes, into the airway. Examples of cytokines that are suppressed through gene suppression activity of steroids are listed in [Box 11.2](#).

Glucocorticoids inhibit many of the cells involved in airway inflammation, including macrophages, T lymphocytes, eosinophils, and mast cells, in the bronchial airway epithelium and submucosa, and reverse the shedding of epithelial cells and goblet cell hyperplasia seen in asthma.^{25,29} By decreasing cytokine-mediated survival of eosinophils, apoptosis of eosinophils occurs, reducing the number of eosinophils in the circulation and in the airway of subjects with asthma. Glucocorticoids also reduce the number of mast cells within the airways; mast cells are sources of histamine and other mediators of inflammation and inhibit plasma exudation and mucus secretion in inflamed airways.^{24,29,30}

Effect on White Blood Cell Count

CLINICAL CONNECTION

An increase in overall white blood cell (WBC) count will be seen in patients receiving systemic corticosteroids (orally, intravenously, or intramuscularly); however, depending on dose of inhaled corticosteroid, the WBC count may remain unchanged.

Leukocytes, such as monocytes, macrophages, neutrophils, and basophils, are also essential to the inflammatory response and are attracted to an area of injury by the chemotactic factors identified among the mediators of inflammation. Neutrophils usually adhere (“marginate”) to the capillary endothelium of storage sites in the lung. Glucocorticoids cause depletion of these stores and reduce their accumulation at inflammatory sites and in exudates. This is termed *demargination* and can increase the number of neutrophils in circulation when the cells leave their storage sites. An overall increase in the WBC count can be seen in patients receiving

glucocorticoids. Glucocorticoids affect other leukocytes by inhibiting the number of monocytes, basophils, and eosinophils; this can also be seen in the differential count of these cells. A person with allergic asthma who would otherwise have a higher than normal eosinophil count would show a low count after initiation of drug therapy. Finally, glucocorticoids constrict the microvasculature to reduce leakage of the previously cited cells and fluids into inflammatory sites.

CLINICAL CONNECTION

The use of systemic and inhaled corticosteroids increases affinity and number of β receptors assisting in the use of bronchodilators, this is termed *upregulation*.

Effect on β Receptors

β -adrenergic agents are among the most potent inhibitors of mast cell release; yet an individual with asthma in an acute episode may be unresponsive to these drugs. A beneficial effect of glucocorticoids is their ability to restore responsiveness to β -adrenergic stimulation.^{21,30} This effect can be seen within 1 to 4 hours after intravenous administration of glucocorticoids and is the rationale for administering a bolus of steroid in status asthmaticus as part of acute treatment. Although steroid action is slow, the sooner steroids are given, the sooner the patient with asthma begins to respond to β -adrenergic drugs, and supported ventilation may be avoided. Glucocorticoids enhance β -receptor stimulation by increasing the number and availability of β receptors on the cell surfaces and by increasing affinity of the receptors for β agonists. There is also evidence that glucocorticoids prolong endogenous circulatory catecholamine action by inhibiting the uptake-2 mechanism. The mechanisms for a positive interaction between β_2 agonists and corticosteroids are described in the discussion on aerosolized corticosteroid agents at the end of the section.

Hazards and Side Effects of Steroids

Systemic Administration of Steroids

KEY POINT

Hazards associated with *systemically* administered steroids include hypothalamic–pituitary–adrenal (HPA) axis suppression, immunosuppression, fluid retention, muscle wasting, and others.

The complicating side effects of systemic steroid treatment are well known and provide the motivation to switch to aerosolized, inhaled steroids, when possible. These complications arise from the physiologic effects of steroids on the body. These physiologic effects are often exaggerated with systemic drug therapy because potency and plasma levels are higher than those with the body's own steroids. Complications of systemic therapy are reviewed by Truhan and Ahmed.³¹ These complications are summarized in [Box 11.3](#) and are briefly described here:

- Suppression of the HPA axis may occur, causing inhibition of ACTH release and cortisol secretion from the adrenal gland. The length of time to recover from this suppression varies with patient, dose, and duration of treatment.
- With sufficient dose and duration, immunosuppression can be caused; this can lead to increased susceptibility to infection by bacterial, viral, or fungal agents.

• BOX 11.3 Side Effects Seen With Systemic Administration of Corticosteroids

- Hypothalamic–pituitary–adrenal (HPA) axis suppression
 - Immunosuppression
 - Psychiatric reactions
 - Cataract formation
 - Myopathy of skeletal muscle
 - Osteoporosis
 - Peptic ulcers
 - Fluid retention
 - Hypertension
 - Increased white blood cell count
 - Dermatologic changes
 - Growth restriction
 - Increased glucose levels
-
- Psychiatric reactions can occur, including insomnia, mood changes, and bipolar or schizophrenic psychoses.
 - Cataract formation has been noted, and rarely, intraocular pressure may increase.
 - Myopathy of striated skeletal muscle can occur.
 - Steroid-induced osteoporosis is debated but is thought to be a limitation of extended steroid therapy. Aseptic necrosis of the bone is also caused by steroid therapy.
 - Peptic ulcer is thought to be a complication, but evidence for this is debated. Patients may often be receiving other ulcerogenic medications, such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs).
 - Fluid retention can occur because of the sodium-sparing effects of glucocorticoids, giving a puffy appearance.
 - Hypertension may accompany the fluid retention or be aggravated by it.
 - Corticosteroids given systemically can increase the WBC count, with an increase in neutrophils and a decrease in lymphocytes and eosinophils.
 - Dermatologic changes can occur, including a redistribution of subcutaneous fat causing the cushingoid appearance of central obesity, humpback, and moon face.
 - Growth of children can be slowed by prolonged systemic therapy because corticosteroids retard bone growth and epiphyseal maturation.
 - Corticosteroids lead to gluconeogenesis and antagonize glucose uptake, causing hyperglycemia. This can lead to reversible steroid-induced diabetes.

Systemic Side Effects With Aerosol Administration

KEY POINT

Hypothalamic–pituitary–adrenal (HPA) axis suppression is minimal or absent with inhaled agents, although high doses can cause adrenal suppression in a dose-dependent fashion.

The rationale for the introduction of inhaled aerosol steroids was to eliminate or reduce the side effects seen with systemic therapy. Although aerosol steroids are administered in low doses because of their high topical activity, local side effects may occur, and certain systemic side effects, listed in Box 11.4, are also a concern. Some side effects may occur with transfer from oral therapy to the inhaled route. Three systemic effects of concern with inhaled

• BOX 11.4 Potential Hazards and Side Effects With Inhaled Aerosol Corticosteroids

Systemic

- Adrenal insufficiency*
- Extrapulmonary allergy*
- Acute asthma*
- HPA axis suppression (minimal, dose dependent)
- Growth restriction (dose dependent)

Local (Topical)

- Oropharyngeal fungal infections
- Dysphonia
- Cough, bronchoconstriction
- Incorrect use of MDI (inadequate dose)

HPA, Hypothalamic–pituitary–adrenal; MDI, metered dose inhaler.

*After transfer from systemic corticosteroid therapy.

steroids are HPA axis suppression, loss of bone density, and growth restriction in children. Possible systemic side effects with inhaled steroids are as follows:

- Adrenal insufficiency may occur after transfer from systemic to inhaled aerosol steroids. Weaning from systemic steroids to allow recovery of adrenal cortex and HPA axis function and careful monitoring of pulmonary function can help control this problem.
- There may be a recurrence of allergic inflammation in other organs, such as nasal polyps or atopic dermatitis, after cessation of systemic steroids.
- Acute severe episodes of asthma may occur after withdrawal from oral steroids and transfer to inhaled forms. Aerosolized steroids may be inadequate to control asthma, especially during periods of stress, and short courses of oral drug may be necessary (“burst” therapy).
- Suppression of HPA axis function is nonexistent or low at small doses of inhaled aerosol steroids and increases with higher doses. Clinically significant suppression is rare at inhaled doses less than 800 mcg/day in adults and less than 400 mcg/day in children.³² Goldberg et al.³³ investigated MDI beclomethasone administration, with and without a reservoir, in children. They found that 7 of 15 subjects using the MDI alone (average dose 474 ± 220 mcg/day) showed adrenal suppression as measured by 24-hour urinary free cortisol excretion. Only 2 of 24 subjects using an MDI-reservoir system (average dose 563 ± 249 mcg/day) showed such suppression. These results indicated that inhalation of low to moderate doses can cause some adrenal suppression and that use of a reservoir can reduce this, probably by reducing the amount of drug swallowed. Although higher inhaled doses of steroid have a greater risk of adrenal suppression, the dose at which the risk for toxicity outweighs the beneficial effect of an inhaled steroid remains unknown.³²
- Questions have been raised about the effect of inhaled steroids on growth when used in prepubertal children. A study by Wolthers and Pedersen³⁴ found a reduction in rate of lower leg growth with inhaled budesonide compared with a placebo. Growth restriction was seen in some studies with beclomethasone dipropionate, but other studies have found no effect on growth with the same drug by inhalation. Results may be confounded by the moderate growth restriction and delay in puberty seen as a result of asthma.³ These authors cited a meta-analysis that found no association between growth impairment

TABLE 11.4 Bioavailability of Oral and Inhaled Corticosteroid Agents

	Oral (%) [*]	Inhaled (%) [†]
Beclomethasone dipropionate	<20	≈20
Triamcinolone acetonide	22.5	21.5
Budesonide	1.0	25.0
Fluticasone propionate	<1	20.0

^{*}Figures represent percentages of a 100% oral dose.

[†]Figures represent the 20% of an inhaled dose that reaches the lungs and indicate complete absorption of that fraction.

Modified from Johnson, M. (1996). Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. *Journal of Allergy and Clinical Immunology*, 97(Suppl), 169.

and inhaled beclomethasone dipropionate, even at higher doses.³⁵ In a study by Richardson and others,³⁶ it was found that the use of beclomethasone and fluticasone results in growth retardation. The benefits of inhaled corticosteroids in the treatment of asthma outweigh the possible consequence of growth retardation, however.

- No data have shown clearly the effect of inhaled glucocorticoids in asthma on bone density and osteoporosis. However, Sutter and Stein³⁷ discovered that the higher the dose of inhaled corticosteroid, the greater was the effect on bone density seen in premenopausal women with asthma.

It is logical that the risks of steroid-induced adverse effects are lower with the relatively low doses of inhaled steroids compared with systemic administration. However, the threshold doses by inhalation causing adrenal suppression or other effects remain unknown. These effects generally are rare with doses of 800 mcg/day or less in adults and 400 mcg/day or less in children. Absorption of inhaled steroid leads to systemic bioavailability from both the swallowed portion and the inhaled portion reaching the lung. Table 11.4 summarizes the data on the bioavailability of four agents. When administered orally, bioavailability ranges from less than 1% to greater than 20% of the total dose; this results from the high first-pass metabolism of the swallowed drug. In contrast, all of the inhaled dose reaching the lung is absorbed and enters the systemic circulation, where it is ultimately metabolized in the liver or extrapulmonary tissues.¹¹ The efficiency of the delivery device in depositing drug in the lungs determines the amount of drug entering the systemic circulation from the airway. Thorsson et al.³⁸ reported that an MDI of budesonide delivered 18% of the dose to the lungs, whereas a DPI preparation (Turbuhaler) delivered nearly twice as much (32%). Leach et al.³⁹ found that HFA formulations gave more than CFC formulations, with 53% of HFA beclomethasone deposited in the lung.

The higher deposition is related to the particle size distribution of the device. HFA inhalers give a much better particle size distribution than CFC devices. Unless lower doses are used with HFA devices and DPIs, greater systemic drug levels result compared with those produced with an equal dose from MDIs. Total bioavailability—and the amount of drug that can cause systemic side effects, such as HPA axis suppression—is a function of the swallowed amount, with its bioavailability, and the inhaled amount, all of which is absorbed into the circulation. Many HFA corticosteroid doses are lower than CFC corticosteroid doses. Use of a reservoir device and mouth rinsing can minimize the oropharyngeal loss and amount of swallowed drug contributing to systemic

bioavailability and potential side effects. It is necessary to adjust doses on the basis of the efficiency of the delivery system and the amount reaching the airway.

Topical (Local) Side Effects With Aerosol Administration

CLINICAL CONNECTION

Inhaled agents may cause local oral candidiasis, hoarseness, cough, and bronchoconstriction in some cases.

Two of the most common side effects caused by topical application of inhaled steroids in the respiratory tract are oropharyngeal candidiasis (oral thrush) and dysphonia. Several other complications and precautions with the inhaled route are summarized below.

Oropharyngeal Fungal Infections

Infections with *C. albicans* or *Aspergillus niger* may occur in the mouth, pharynx, or larynx because of aerosolized steroid treatment. Some form of this may be seen in one third of patients taking the aerosol formulations; however, these infections respond to topical antifungal agents and seem to diminish with continued aerosol steroid use.⁸ Occurrence and severity are dose related and are more likely to occur in patients who are also taking oral steroids. The use of a spacer device and gargling after treatment can reduce oropharyngeal deposition of the steroid and the incidence or severity of oropharyngeal fungal infections.

Dysphonia

Hoarseness and changes in voice quality may also occur with inhaled steroids in one third of patients. This dysphonia can be minimized by use of a spacer and by gargling. The effect is caused primarily by adductor vocal cord paresis, which is thought to be a local steroid-induced myopathy.⁴⁰

Other Complications or Precautions

- **Cough and bronchoconstriction:** Occasionally, cough or bronchoconstriction may occur after inhalation of an aerosol steroid.⁸
- **Incorrect use:** Incorrect use of the MDI delivery vehicle represents a possible risk factor because inadequate amounts of the topical inhaled steroid are delivered.
- With inhaled steroids, the following can minimize the risk of local and systemic adverse effects:
 - Use of minimal doses (400 mcg/day in children and 800 mcg/day in adults), or the lowest effective dose
 - Use of a reservoir device
 - Mouth rinsing after treatments

CLINICAL CONNECTION

Side effects with inhaled steroids can be minimized by use of a reservoir device, rinsing of the mouth after treatments, and use of minimal doses.

Clinical Application of Aerosol Steroids

Corticosteroids are used for a wide variety of conditions with the therapeutic goal of reducing inflammation. These applications include clinical conditions, such as contact dermatitis, rheumatoid arthritis, and systemic lupus erythematosus, as well as asthma

and COPD, and include topical cream application and oral, parenteral, and inhaled formulations.

Use in Asthma

KEY POINT

Inhaled steroids are used in asthma as a first-line therapy for mild to moderate asthma.

The 2022 Global Initiative for Asthma (GINA)⁴ and the Expert Panel¹ on Asthma, identify corticosteroids as long-term control agents rather than quick-relief agents. However, the use of combination agents such as budesonide/formoterol have been shown to be effective as a rescue agent in adults. Corticosteroids traditionally have been used in asthma by the oral route for maintenance therapy of severe asthma, by the oral or intravenous route for treatment of status asthmaticus, and by inhalation for maintenance of asthma control. However, increased emphasis on asthma as a disease of inflammation leading to bronchial hyperresponsiveness has shifted the use of inhaled aerosol steroids from second-line or third-line therapy to first-line, primary therapy. The use of corticosteroids can control asthma and improve asthma symptoms by reducing exacerbations and improving lung function.¹

The principles of corticosteroid use in asthma, based on the previously mentioned guidelines, are summarized below:

- Bronchial hyperresponsiveness is characteristic of asthma and is related to the degree of airway inflammation.
- The basic pathology of asthma, previously emphasized as bronchospasm, is now understood to be a chronic inflammatory disorder of the airways resulting from a complex interaction among inflammatory cells, mediators, and airway tissue.¹ The phrase “chronic desquamating eosinophilic bronchitis” has been used to describe asthma.⁸
- Inhaled corticosteroids are the most effective long-term therapy for mild, moderate, or severe persistent asthma, and they are well tolerated and safe at recommended dosages.^{1,4} Several points are related to the use of inhaled steroids:
 - Barnes⁴¹ suggested starting inhaled corticosteroids at a high-enough dose to be effective and then reducing the dose. Alternatively, a short course of systemic corticosteroids can be used to gain control of symptoms followed by a step-down in therapy.¹ Loss of patient confidence and compliance with prescribed use of inhaled corticosteroids may be avoided in this way, especially because steroids do not give an immediate effect as a bronchodilator does. Any reduction in pharmacologic management should be monitored by symptoms, concomitant need for β_2 agonists, and peak flow rates.
 - An increase in dose of inhaled corticosteroids, such as doubling of the current dose, if PEF rates decline 25% to 30% may avoid the need for oral steroids. However, controlled studies are needed to confirm the effectiveness of such practices.⁴¹
 - If asthma is not controlled by inhaled corticosteroids and other types of drug therapy, a short burst of oral steroids may be required to regain control of the asthma and to help clear the airways.^{1,9}

Early Use of Corticosteroids in Asthma

There is evidence that the addition of an inhaled corticosteroid to first-line β -agonist maintenance treatment of asthma reduces morbidity and airway hyperresponsiveness.^{1,42} Haahtela et al.⁴³ showed that subjects with mild asthma maintained on inhaled budesonide (1200 mcg/day for 2 years and then 400 mcg/day) had decreased

bronchial response to histamine challenge compared with subjects taking inhaled terbutaline (375 mcg twice daily) over a 2-year period. Perhaps the most significant finding was that the later addition of inhaled budesonide after use of a β_2 agonist was unable to give as high a level of bronchoprotection as achieved by subjects who had started with and continued taking the inhaled steroid. This finding suggests that irreversible changes had occurred during the 2 years of β_2 -agonist therapy and supports earlier use of inhaled steroids.

Pauwels et al.⁴⁴ found that early treatment in mild persistent asthma with low-dose corticosteroids decreased exacerbations, increased symptom-free days, improved FEV₁, and decreased the need for systemic corticosteroids. In a meta-analysis, Masoli et al.⁴⁵ reported that inhaled corticosteroids are best in treating asthma when kept to a therapeutic range of 400 mcg/day. Although inhaled corticosteroids are first-line antiinflammatory agents and acceptable for primary therapy of moderate asthma in children, the antiasthma prophylactic agents cromolyn sodium, nedocromil sodium, and leukotriene modifiers may be used as an initial choice for long-term control therapy of mild persistent asthma (step 2 therapy) in children because these medications have excellent safety profiles.¹

Inhaled Corticosteroids for Acute Severe Asthma

Inhaled corticosteroids have not been considered useful for treatment of acute, severe asthma episodes, and drug labeling contraindicates this use because there is no bronchodilator effect. In addition, the dose of inhaled steroids is low compared with oral administration. A study by Rodrigo and Rodrigo⁴⁶ examined the addition of high, cumulative doses of inhaled flunisolide added to albuterol in emergency department treatment of acute adult asthma. Both drugs were given via an MDI with a spacer. Flunisolide was given as four puffs (250 mcg/actuation) every 10 minutes. Their protocol allowed 3 hours of this treatment, with a cumulative dose of 6 mg of flunisolide each hour, and equally aggressive albuterol dosing. The use of flunisolide resulted in better lung function at 90 minutes and afterward compared with the use of albuterol alone. Although preliminary, these results suggest that the contraindication to the use of inhaled corticosteroids for treating acute severe asthma may need to be reconsidered.

Clinical Use of Inhaled Corticosteroids

Other considerations in the clinical application of inhaled corticosteroids are as follows:

- High-dose inhaled steroids can be tried in cases of severe, persistent asthma to replace or reduce oral corticosteroid dependence. High doses of inhaled steroids are two to four times the usual recommended dose. Oral steroid therapy can be reduced slowly while monitoring the patient's pulmonary function.¹ Although more control may be achieved with high doses of inhaled steroids, side effects, including systemic effects, are also likely to increase with inhaled doses greater than 1 mg/day. However, if oral steroids can be replaced or even reduced, this can be an overall improvement in the risk-to-benefit ratio.
- MDI-formulated corticosteroids should be administered for oral inhalation using a reservoir device (preferably a holding chamber rather than a spacer), and all formulations should include mouth rinsing to reduce the risk of oropharyngeal candidiasis or other fungal infections and to reduce systemic absorption from swallowed drug.
- Use of a long-acting β_2 agonist, such as salmeterol, in subjects who have inadequate symptom control and are already receiving low to moderate doses of inhaled corticosteroids may prevent the need to increase the inhaled corticosteroid dose.¹

- The use of long-term β -agonist therapy with a corticosteroid can improve lung function.¹
- Compliance with prescribed steroid therapy by inhalation seems to be poor and can be a complicating factor in the management of asthma and COPD. The ability to reduce agents or move to once-a-day dosing may be helpful.

Use in Chronic Obstructive Pulmonary Disease

KEY POINT

Glucocorticoids may be useful in chronic obstructive pulmonary disease (COPD) and are often administered systemically for acute exacerbations. Inhaled glucocorticoids are prescribed for long-term results.

CLINICAL CONNECTION

Corticosteroid use in chronic obstructive pulmonary disease (COPD) predisposes patients to infections, such as pneumonia.

The use of steroids in COPD is recognized as having potential action in relieving symptoms and exacerbations, but steroid use has little to no effect on FEV₁. The use of corticosteroids is described in the 2020 ATS guidelines² and in the 2022 GOLD guidelines.³ A review and update on COPD have been provided by Hatipoğlu and Aboussouan.⁴⁷

COPD is characterized by a different pattern of inflammatory cells than is seen in asthma.^{48,49} Eosinophils predominate in asthma, whereas neutrophils predominate in COPD. Oral and inhaled corticosteroids do not influence the inflammatory changes driven by neutrophils.^{26,48,49}

Available studies show that corticosteroid use in COPD reduces exacerbations, symptoms, and mortality⁵⁰ but has little effect on pulmonary function results.^{51–53} Other studies have found that inhaled corticosteroids may not protect as well against exacerbations, but slow the decline of FEV₁.^{54,55}

In acute exacerbations of COPD, oral or parenteral steroids are often given. Short-term corticosteroid therapy has shown benefits in hospitalized patients.^{3,4} Maltais et al.⁵⁶ found that 2 mg of liquid nebulized budesonide improved FEV₁ compared with a placebo and had similar results to 30 mg of oral prednisolone. Use of inhaled corticosteroids is much safer than oral steroid use. Patients with stable COPD should not be given systemic corticosteroids.²

RESPIRATORY CARE ASSESSMENT OF INHALED CORTICOSTEROID THERAPY

Before Treatment

- Instruct patient in correct use of the aerosol delivery system (MDI, holding chamber, SVN, or DPI), and then verify.
- Assess breathing rate and pattern.
- Assess breath sounds by auscultation before and after treatment.
- Assess pulse before and after treatment.
- Assess patient's subjective reaction to treatment for any change in breathing effort or pattern.

During Treatment and Short Term

- Verify that patient understands that a corticosteroid is a controller agent and is aware of its difference from a rescue bronchodilator (relieving agent); assess patient's understanding of the need

for consistent use of an inhaled corticosteroid (compliance with therapy).

- In asthma, instruct patient in use of a peak flow meter to monitor baseline PEF and changes. Verify that there is a specific action plan, based on symptoms and peak flow meter results. Patient should be clear on when to contact a physician with deterioration in PEF or exacerbation of symptoms.

Long Term

- Assess severity of symptoms (coughing, wheezing, nocturnal awakenings); symptoms during exertion; use of rescue bronchodilator; number of exacerbations; missed work or school days; and pulmonary function. Modify level of therapy with reference to NAEPP or GINA guidelines for asthma and ATS or GOLD guidelines for COPD.
- Assess for presence of side effects with inhaled steroid therapy (oral thrush, hoarseness or voice changes, cough or wheezing with MDI use); have patient use a reservoir (preferably a holding chamber) with MDI use and verify correct use.

General Contraindications

- In general, corticosteroids are safe. However, best practice is use of lowest effective dose.
- Patients should rinse mouth after inhalation of a corticosteroid.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify all corticosteroids, using generic names approved in the United States for clinical use by oral inhalation.
2. What is the major therapeutic effect of corticosteroids?
3. Name two common respiratory diseases in which inhaled corticosteroids are prescribed.
4. What is the rationale for administering corticosteroids by the inhalation route, rather than by the oral route, in asthma?
5. Contrast the effects of β agonists with the effects of corticosteroids on the early phase and late phase of asthma.
6. What is the effect of orally administered corticosteroids on growth, bone density, and adrenal function?
7. What is the purpose of alternate-day steroid therapy?
8. Can you switch from oral steroid use to inhaled steroid use in a patient with asthma? Explain the precautions or reasons, as appropriate.
9. State two common side effects with inhaled steroids.
10. Identify two methods of minimizing the side effects identified in Question 9.
11. Have inhaled corticosteroids traditionally been used with an asthmatic during an acute episode?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 55-year-old White woman presents to the emergency department with a chief complaint of cough, wheezing, shortness of breath, and chest pain. She is well nourished and educated. She is known to have asthma, with one hospitalization in the previous year for asthma exacerbation. She reported experiencing rhinorrhea, sore throat, sinus congestion, and subsequent increase in dyspnea and wheeze 2 days earlier.

Physical examination on admission to the emergency department revealed wheezing on auscultation, use of accessory muscles, no cyanosis or diaphoresis, and mild respiratory distress. Vital signs were as follows:

temperature (T) of 98.4°F, pulse (P) of 96 beats/min, regular, respiratory rate (RR) of 22 breaths/min, and blood pressure (BP) of 92/68 mm Hg.

A chest radiograph showed hyperinflation but no infiltrates or other abnormalities. An electrocardiogram revealed sinus tachycardia. Arterial blood gas determination on room air indicated the following: pH of 7.44, arterial carbon dioxide pressure (PaCO₂) of 38 mm Hg, arterial oxygen pressure (PaO₂) of 54 mm Hg, base excess (BE) at 2.2, bicarbonate (HCO₃⁻) of 25.9 mEq/L, and arterial oxygen saturation (SaO₂) of 89.4%. Hemoglobin was at 13.3 g/dL, and the white blood cell (WBC) count was $8.8 \times 10^3/\text{mm}^3$. Administration of MDI albuterol by reservoir showed little improvement in her peak flow rates.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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12

Nonsteroidal Antiasthma Agents

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CHAPTER OUTLINE

Clinical Indications for Nonsteroidal Antiasthma Agents

Identification of Nonsteroidal Antiasthma Agents

Mechanisms of Inflammation in Asthma

Immunologic (Allergic) Response

Cromolyn-Like (Mast Cell–Stabilizing) Agents

Cromolyn Sodium (Disodium Cromoglycate)

Dosage and Administration

Mechanism of Action

Pharmacokinetics

Clinical Efficacy of Cromolyn Sodium

Clinical Application of Cromolyn Sodium

Antileukotriene Agents

Leukotrienes and Inflammation

Cell Sources of Leukotrienes

Biochemical Pathways

Leukotriene Production

Cysteinyl Leukotriene Receptors and Effects of Leukotrienes

Zileuton (Zyflo)

Dosage and Administration

Mechanism of Action

Pharmacokinetics

Hazards and Side Effects

Zafirlukast (Accolate)

Dosage and Administration

Mechanism of Action

Pharmacokinetics

Hazards and Side Effects

Montelukast (Singulair)

Dosage and Administration

Mechanism of Action

Pharmacokinetics

Hazards and Side Effects

Role of Antileukotriene Drugs in Asthma Management

Protection Against Specific Asthma Triggers

Chronic Persistent Asthma

Antileukotrienes in Relation to Corticosteroids

Churg-Strauss Syndrome

Summary of Clinical Use of Antileukotriene Therapy

Monoclonal Antibodies

Dosage and Administration

Mechanism of Action

Hazards and Side Effects

Summary of Clinical Use of Monoclonal Antibodies

Respiratory Care Assessment of Nonsteroidal Antiasthma Agents

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Discuss the indications for nonsteroidal antiasthma agents
2. List available nonsteroidal antiasthma agents used in respiratory therapy
3. Differentiate between the specific nonsteroidal antiasthma agents
4. Describe routes of administration available for various nonsteroidal antiasthma agents
5. Describe the mechanism of action for various nonsteroidal antiasthma agents
6. Discuss the use of nonsteroidal antiasthma agents in the treatment of asthma

KEY TERMS AND DEFINITIONS

Antileukotrienes Agents that block the inflammatory response in asthma.

Immunoglobulin E (IgE) Gamma globulin that is produced by cells in the respiratory tract.

Leukotrienes Chemical mediators that cause inflammation.

Mast cells Connective tissue cells that contain heparin and histamine.

Mast cell stabilizers Also known as *cromolyn-like agents*, agents used prophylactically to treat the inflammatory response in asthma.

In Chapter 11, the concept of airway inflammation was introduced to present the antiinflammatory actions of glucocorticoids, and some of the numerous cells and chemicals involved in an inflammatory response were described. This chapter presents drug groups that also have an antiinflammatory effect through mechanisms different from those of the corticosteroids. Three subgroups of agents are included in the nonsteroidal antiasthma group: cromolyn-like drugs (**mast cell stabilizers**), **antileukotrienes**, and monoclonal antibodies. A summary of the immune mechanisms involved in allergic responses is given as an introduction to the specific mechanisms of action for the drug groups discussed in this chapter.

Clinical Indications for Nonsteroidal Antiasthma Agents

The general indication for clinical use of nonsteroidal antiasthma agents described in this chapter is *prophylactic* management (control) of mild persistent asthma (asthma requiring step 2 care, according to the classification presented in the 2007 National Asthma Education and Prevention Program [NAEPP] guidelines¹).

The following are qualifications to the general indication for use of these agents:

- Cromolyn and antileukotrienes are alternatives to low-dose inhaled corticosteroids in asthma requiring step 2 care.¹
- Cromolyn is often used with infants and young children as an alternative to inhaled corticosteroids in asthma requiring step 2 care because of the safety profiles of inhaled corticosteroids.¹
- Antileukotrienes can be beneficial when used in combination with inhaled corticosteroids to reduce the dose of the steroid.

All the nonsteroidal antiasthma drugs described in this chapter are controllers, not relievers, and are used in asthma requiring antiinflammatory drug therapy. **Box 12.1** summarizes reliever and controller agents used in drug therapy for asthma, listing cromolyn sodium, antileukotrienes, and monoclonal antibodies as controllers. Use of rescue β_2 -agonist agents more than twice a week (i.e., asthma requiring step 2 care) is an indicator of the need to initiate controller drug therapy.

Identification of Nonsteroidal Antiasthma Agents

Individual agents in the cromolyn-like agent group, antileukotriene group, and monoclonal antibody group are presented in

• BOX 12.1 Drug Groups Used in Pharmacologic Management of Asthma (Categorized as Controllers or Relievers)

Controllers

Inhaled corticosteroids
Oral corticosteroids
Cromolyn sodium
Long-acting inhaled β_2 agonists
Long-acting oral β_2 agonists
Leukotriene modifiers
Sustained-release theophylline
Monoclonal antibodies (omalizumab)

Relievers

Short-acting inhaled β_2 agonists
Systemic corticosteroids (oral burst therapy, intravenous)
Inhaled anticholinergic bronchodilators

Table 12.1, with generic and brand names, formulations and strengths, and usual recommended dosages.

Mechanisms of Inflammation in Asthma

KEY POINT

Asthma is an inflammatory disorder of the airways in which allergic stimuli often trigger immunoglobulin E (IgE)-mediated mast cell release of mediators of inflammation. Airway reactivity can also be triggered by nonspecific stimuli, such as cold air or dust.

Asthma is a chronic inflammatory disorder of the airways.¹ Asthma has been divided into extrinsic and intrinsic forms based on the triggers for asthma. *Extrinsic* asthma is dependent on allergy, or *atopy*, whereas *intrinsic* asthma shows no evidence of sensitization to common inhaled allergens.² The allergic form of asthma, which is **immunoglobulin E (IgE)** mediated, is associated with younger subjects, and the intrinsic, or nonallergic, form is associated with later onset in adults in whom childhood asthma may not have been present. Corren³ described asthma as an “evolving paradigm” disease in childhood, when viruses are an important trigger, whereas in school-age and teenage years, allergens stimulate an immune response. As asthma progresses and in adults, the disease becomes intrinsic and may be driven by T cells (lymphocytes) that release various cytokines, as described in Chapter 11. Asthma is chronic and persistent, with continuous inflammation and episodes of acute obstruction.

In both forms of asthma, allergic and nonallergic mediators and enzymes are released to act on target tissues in the airway, and cells involved in inflammation are recruited and activated in the airway. Airway inflammation manifests as bronchoconstriction, airway swelling, mucus secretion and obstruction and subsequent airway wall remodeling that furthers the responsiveness of the airway.⁴

KEY POINT

The clinical result of asthma is chronic persistent airway inflammation and occasional acute episodes of wheezing and airway obstruction caused by bronchoconstriction, mucosal swelling, and mucus secretion.

Immunologic (Allergic) Response

Most instances of asthma are primarily an allergic response, which involves **mast cells** and IgE.¹ The immunologic response is outlined in **Box 12.2**. An understanding of the immune response is fundamental to discussing asthma and the mediator antagonists presented in this chapter because allergy is essentially a mistaken immune response.

Generation of an immune response and specifically an allergic asthmatic response is considered to be *initiated* by the interaction of T lymphocytes with an antigen presented by other cells, such as macrophages or B lymphocytes.⁴ Activation of T lymphocytes results in production of IgE by B lymphocytes. Antigen-specific IgE binds to effector cells such as mast cells and is termed a *cytophilic* antibody because of this. When activated by subsequent exposure to an antigen or allergen, mast cells release physiologically active mediators of inflammation, such as prostaglandins, **leukotrienes**, proteases, histamine, platelet-activating factor (PAF), and certain cytokines.⁴ The cytokines released, which include tumor necrosis factor-alpha (TNF- α) and interleukin-4 (IL-4), can upregulate endothelial adhesion molecules.³

TABLE 12.1 Nonsteroidal Antiasthma Medications: Generic and Brand Names, Formulations, and Usual Recommended Dosages*

Generic Drug	Brand Name	Formulation and Dosage
Cromolyn-Like Agents (Mast Cell Stabilizers)		
Cromolyn sodium	Generic only	Small volume nebulizer (SVN): 20 mg/ampule or 20 mg/2 mL (1%) Adults and children ≥ 2 yr: 20 mg inhaled 4 times daily Spray: 5.2 mg per actuation. Available over the counter (OTC) Adults and children ≥ 2 yr: 1 spray in each nostril, 3–6 times daily, every 4–6 hr Oral concentrate: 100 mg/5 mL Adults and children ≥ 13 yr: 2 ampules 4 times daily, 30 min before meals and at bedtime Children 2–12 yr: 1 ampule 4 times daily, 30 min before meals and at bedtime
Antileukotrienes		
Zafirlukast	Generic; Accolate	Tablets: 10 and 20 mg Adults and children ≥ 12 yr: 20 mg twice daily, without food Children 5–11 yr: 10 mg twice daily
Montelukast	Generic; Singulair	Tablets: 10 mg and 4- and 5-mg cherry-flavored chewable; 4-mg packet of granules Adults and children ≥ 15 yr: One 10-mg tablet daily Children 6–14 yr: One 5-mg chewable tablet daily Children 2–5 yr: One 4-mg chewable tablet or one 4-mg packet of granules daily Children 6–23 mo: One 4-mg packet of granules daily
Zileuton	Generic; Zflo; Zflo CR	Tablets: 600 mg Adults and children ≥ 12 yr: One 600-mg tablet 4 times per day; CR, two tablets twice daily, within 1 hr of morning and evening meals
Monoclonal Antibody		
Omalizumab	Xolair	Adults and children ≥ 6 yr: SQ every 4 wk; dose depends on weight and serum IgE level
Benralizumab	Faserna	Adults and children ≥ 12 yr: SQ: 30 mg, Q4 wk
Mepolizumab	Nucala	Adults and children ≥ 6 yr: SQ: 40–100 mg, Q4 wk
Reslizumab	Cinqair	Adults and children ≥ 18 yr: IV: 3 mg/kg, Q4 wk
Dupilumab	Dupixent	Adults and children ≥ 6 yr: SQ: Initial 200–600 mg, then 200–300 mg every 2–4 weeks
Tezupelumab-ekko	Trespire	Adults and children >12 yr: SQ: 210 mg every 4 weeks

*Detailed prescribing information should be obtained from manufacturer's package insert.
IgE, Immunoglobulin E; IV, intravenous injection; SQ, subcutaneous injection.

• BOX 12.2 Overview of Immune Mechanisms Involved in Allergy and Inflammation

Cell-Mediated

T lymphocytes (from bone marrow stem cells, processed in the thymus) mediate the immune response by several mechanisms, including cytotoxicity and secretion of cytokines. Members of the family of T lymphocytes are the basis of cellular immunity:

- **Helper/T4 (CD4+) cells**, which are subdivided into the following:
 - **Type 1 (Th1) cells**: Regulate classic delayed-type hypersensitivity reactions and other actions related to macrophage activation and T cell–mediated immunity by the production of interferon- γ and interleukin-2 (IL-2)
 - **Type 2 (Th2) cells**: Translate mRNAs for IL-4 and IL-5 and are involved in atopic allergy. IL-4 is essential for production of immunoglobulin E (IgE) by B cells; IL-5 and granulocyte macrophage–colony-stimulating factor (GM-CSF) and IL-3 promote eosinophil maturation, activation, and survival
- **Suppressor/T8 (CD8+) cells**: Inhibit immune response to an antigen after the immune response has begun
- **Cytotoxic T cells**: Bind to viral antigen on the surface of infected cells to destroy the cells

- **Natural killer cells**: Lymphocytes related to cytotoxic T cells; their targets are thought to be tumor cells or cells infected with organisms other than viruses

Antibody-Mediated

Antibodies are serum globulins (proteins) modified specifically to combine and react with an antigen (substance capable of provoking antibodies or cellular immunity).

- **B lymphocytes**: Antibody-producing plasma cells; memory cells for later antibody production
- **Classes of antibody**: Classes of immunoglobulins are as follows:
 - Immunoglobulin G (IgG)
 - Immunoglobulin A (IgA)
 - Immunoglobulin M (IgM)
 - Immunoglobulin D (IgD)
 - Immunoglobulin E (IgE): Cytophilic antibody (binds to effector cells, such as mast cells); termed *reagin antibody*; involved in allergic responses and atopy

This cascade of mediators causes an inflammatory response manifesting as vascular leakage, bronchoconstriction, mucus secretion, and mucosal swelling, all of which obstruct airflow in the bronchioles. T lymphocytes also release cytokines (e.g., interleukins), causing accumulation and activation of eosinophils, which also release chemicals to damage the airway. The process of initiating the inflammatory response and continuing it through amplification, as discussed next, is illustrated in Fig. 12.1.

After being initiated by exposure to antigen, the inflammatory response in the airway is *amplified* by chemoattraction of more lymphocytes, eosinophils, basophils, and neutrophils and by an increase in mast cells. Adhesion molecules increase after stimulation of lymphocytes and mast cells by antigen or allergen. These molecules, found in epithelial cells (intercellular adhesion molecule-1 [ICAM-1]) and vascular endothelial cells (vascular cell adhesion molecule-1 [VCAM-1]) in the airway, are responsible for eosinophil, neutrophil, and lymphocyte recruitment from the microvascular circulation into the airways. The adhesion molecules enable leukocytes to marginate, cross the blood vessel wall, and migrate to the airway mucosa, continuing and further amplifying the inflammation that has begun.⁵ The increase and activation of eosinophils are associated with increased inflammation and severity in asthma.³

Nonspecific stimuli, such as fog, sulfur dioxide, dust, and cold air, can stimulate sensory receptors and cause reflex bronchoconstriction⁴ (see Chapter 7). Patients with asthma are more sensitive to such stimuli, and this reflects altered neural control, chronic inflammation sensitizing the airway, or both. Nerve fibers of the noncholinergic, nonadrenergic excitatory system, containing potent peptide mediators, contribute to local effects on smooth muscle and mucous glands and reflexively stimulate cholinergic activity. Some of these peptides include substance P (SP),

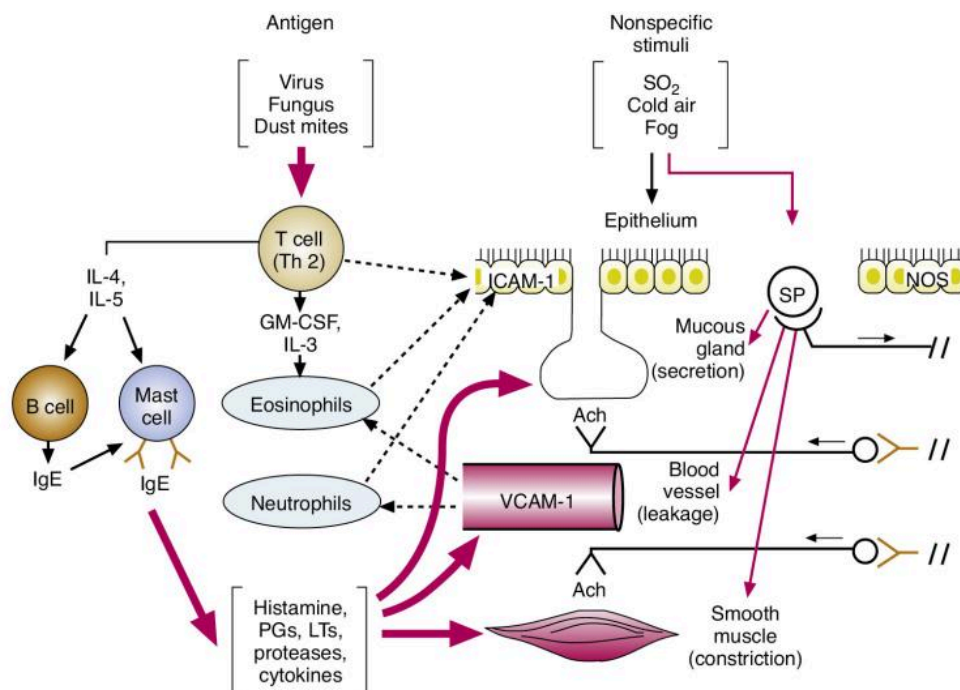
neurokinin A (NKA), and neurokinin B (NKB); they are released from sensory C-fiber nerve endings. These neuropeptides can also contribute to inflammation and the features of asthma previously described, such as mucus hypersecretion, smooth muscle contraction, plasma leakage, inflammatory cell activation, and adhesion. Neutral endopeptidase (NEP) is an enzyme that inactivates neuropeptides to limit their activity; NEP is found on the surface of cells that contain receptors for neuropeptides (smooth muscle, airway epithelium, and vascular endothelium). An increased release of excitatory neuropeptides may be involved in asthma.⁴

Nitric oxide is formed in airway tissue through the action of the enzyme nitric oxide synthase (NOS). There is evidence that in asthma NOS is upregulated in airway epithelium.⁴ Nitric oxide, a potent vasodilator and bronchodilator, may be the neurotransmitter for the nonadrenergic, noncholinergic inhibitory nervous system (see Chapter 5). Nitric oxide, which can damage cells, possibly is induced by proinflammatory cytokines in asthma and contributes to the observed epithelial damage,^{5,6} as shown in Fig. 12.1.

A better understanding of the inflammatory process just described has spurred the development of drugs targeted at interrupting the inflammatory processes and blocking the asthmatic response. These drugs include cromolyn sodium, a mast cell stabilizer; montelukast, zafirlukast, and zileuton, which are antileukotrienes; and omalizumab, a monoclonal antibody.

KEY POINT

Allergic inflammation of the airway is the product of an immune response, and the T lymphocyte plays a central role in attracting mast cells and eosinophils, which, in turn, release mediators that attract other cells and damage epithelial cells.



• **Fig. 12.1** Illustration of complex interaction of cells and mediators that are thought to initiate and amplify inflammation of the airway in asthma, resulting in acute episodes of bronchoconstriction and persistent airway damage. *Ach*, Acetylcholine; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *ICAM-1*, intercellular adhesion molecule-1; *IgE*, immunoglobulin E; *IL-3*, *IL-4*, *IL-5*, interleukin-3, interleukin-4, interleukin-5; *LTs*, leukotrienes; *NOS*, nitric oxide synthase; *PGs*, prostaglandins; *SO₂*, sulfur dioxide; *SP*, substance P; *Th2*, helper T cell type 2; *VCAM-1*, vascular cell adhesion molecule-1.

Cromolyn-Like (Mast Cell–Stabilizing) Agents

Cromolyn sodium, also termed *disodium cromoglycate*, is used as an inhaled prophylactic aerosol drug to prevent the inflammatory response in asthma. These drugs differ in structure and activity from the drug groups considered in previous chapters. Their chemical structures are illustrated in Fig. 12.2. The basic catecholamine xanthine and steroid structures are given for comparison. Cromolyn is not related to the β agonists, xanthines, theophylline, or antiinflammatory glucocorticoids. Cromolyn has no intrinsic bronchodilating capability.

Cromolyn Sodium (Disodium Cromoglycate)

Cromolyn sodium is used as a prophylactic agent in the treatment of asthma. Although it may not be used as often in clinical practice today as it was previously, this agent is an alternative in mild persistent asthma.¹ The antiinflammatory, mast cell–stabilizing effect of cromolyn has led to uses other than asthma prophylaxis, including the following:

- Allergic rhinitis (nasal solution)
- Mastocytosis—to improve diarrhea, abdominal pain, headaches, nausea, and itching (oral)

Administration and dosage for these alternative applications are presented briefly in the next section, along with inhaled formulations for asthma and allergic rhinitis.

Dosage and Administration

Table 12.1 lists the inhaled, oral, and nasal formulations of cromolyn sodium and the recommended doses.

Solution for Nebulization. The ampule or vial contains 20 mg in 2 mL of aqueous solution (a 1% strength). This solution can be nebulized in any small reservoir device powered by compressed air to produce suitably small particles of 3 to 5 μ m in size. Additional diluent may be needed for most nebulizers to function well. Slow tidal breathing reduces the need for inspiratory maneuvers as seen with the metered dose inhaler (MDI), although longer administration times and lack of portability become a disadvantage.

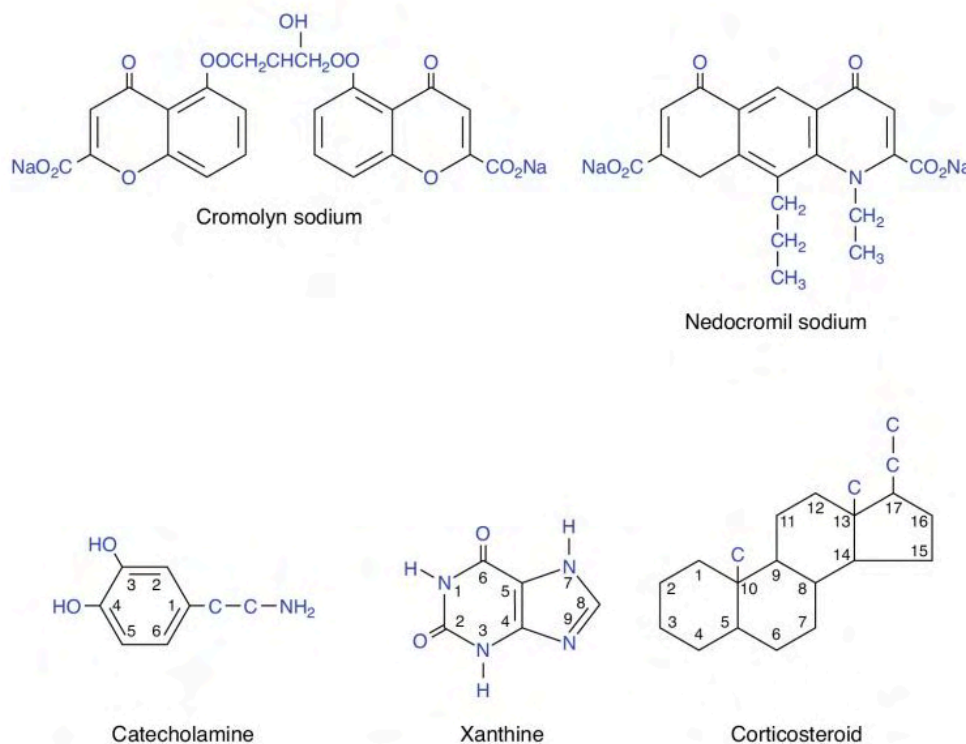
Metered Dose Inhaler. The chlorofluorocarbon (CFC) version of cromolyn sodium was removed from the market as of December 31, 2010.

Nasal Solution (NasalCrom). Cromolyn is available as 5.2 mg per actuation for treatment of seasonal and perennial allergic rhinitis. As with the inhaled solution, protection requires prior administration, although the drug does not need to be taken outside of seasonal exposure to allergens. The solution is delivered by means of a metered pump spray device that is available over the counter (OTC).

Mechanism of Action

Cromolyn sodium is considered an antiasthma agent, an antiallergy agent, and a mast cell stabilizer. Pretreatment with inhaled cromolyn sodium results in inhibition of mast cell degranulation, blocking release of the chemical mediators of inflammation (Fig. 12.3). By its action, cromolyn is effective in blocking the late-phase reaction in asthma. (The late-phase reaction in asthma is discussed in the review of corticosteroids in Chapter 11.)

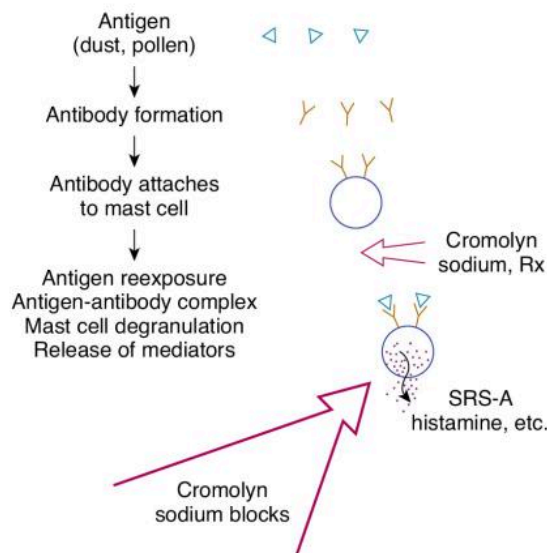
Cromolyn prevents the extrusion of granules containing the mediators of inflammation to the cell exterior. For this reason, cromolyn is often classified as a mast cell stabilizer. The exact mechanism by which this inhibition is accomplished is not completely



• **Fig. 12.2** Chemical structures of cromolyn sodium (disodium cromoglycate) compared with basic catecholamine, xanthine, and corticosteroid structures.

understood, but the following details of cromolyn activity and mast cell function are known:

- The mechanism of action of cromolyn sodium is *prophylactic*; pretreatment is necessary for inhibition of mast cell degranulation.
- Cromolyn sodium may inhibit mediator release by preventing calcium influx necessary for microfilament contraction and extrusion of mast cell granules.
- Cromolyn sodium does not have an antagonist effect on any of the chemical mediators themselves.
- Cromolyn sodium does not operate through the cyclic adenosine 3',5'-monophosphate (cAMP) system and does not affect α or β receptors.
- Antibody formation, attachment of antibodies (IgE) to the mast cell, and antigen-antibody union are *not* prevented by cromolyn; cromolyn does prevent release of mediators.
- Cromolyn sodium can prevent or attenuate the late-phase response in an asthma episode, which can otherwise cause more severe airway obstruction 6 to 8 hours after initial bronchoconstriction.



• **Fig. 12.3** Mechanism of action of cromolyn sodium in preventing mast cell degranulation. SRS-A, Slow-reacting substance of anaphylaxis, consisting of leukotrienes C_4 , D_4 , and E_4 .

The protective effect of cromolyn in inhibiting mast cell degranulation has been captured by scanning electron microscopy and is shown in the sequence in Fig. 12.4. Initial understanding of the activity of cromolyn focused on allergy-triggered mast cell release of mediators, and the drug came to be considered useful primarily in allergic asthma. There is evidence that the activity of cromolyn is not limited to preventing allergen-stimulated asthma. Cromolyn inhibits mast cell mediator release caused by nonallergic stimuli and may reduce reflex-induced asthma. The latter requires about twice the usual dose of cromolyn. Understanding of the broader protection given by cromolyn has supported its successful use in allergic and nonallergic asthma and specifically in exercise-induced asthma.

Pharmacokinetics

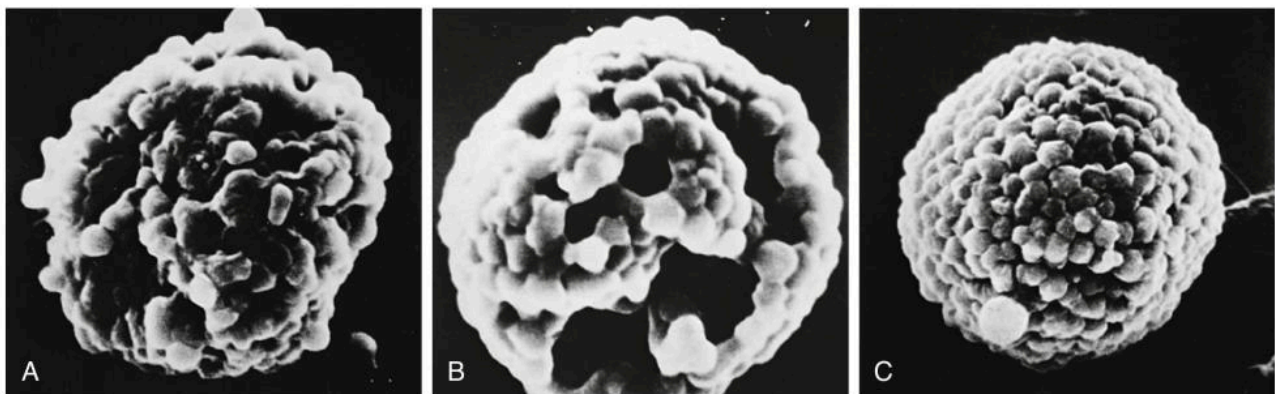
As with other inhaled aerosols, cromolyn sodium is distributed to the airway and to the stomach via a swallowed portion. Distribution to the stomach (swallowed portion) can be modified by use of reservoir devices with the MDI formulation. The dose reaching the airway is absorbed from the lung and quickly excreted unchanged in bile and urine. The lung portion does not seem to be metabolized in the airway. The swallowed portion is largely unabsorbed from the gastrointestinal tract and excreted in feces.

Cromolyn sodium is a safe drug. It has an effectiveness similar to theophylline in controlling asthma, with a better therapeutic margin compared with theophylline.¹ Nasal congestion may be seen after beginning cromolyn sodium use. Dermatitis, myositis (muscle tissue inflammation), and gastroenteritis have been observed to occur in a very few patients.

Use of the *nebulizer solution* has been associated with cough, nasal congestion, wheezing, sneezing, nasal itching, epistaxis, or nose burning. Use of the *nasal solution* has most commonly been associated with sneezing, nasal stinging or burning, and a bad taste. Side effects of the *oral capsules* for mastocytosis are difficult to differentiate from the effects of the disease itself. Adverse events with this use of cromolyn sodium were transient and included headache and diarrhea.

Clinical Efficacy of Cromolyn Sodium

The NAEPP guidelines provide several studies describing the effectiveness of cromolyn sodium.¹ However, the guidelines do point out that other studies have not found it to be effective in the treatment of asthma. In their review of 23 studies,



• **Fig. 12.4** Degranulation of a mast cell. **A**, Mast cell undergoing gross degranulation shows free granules. **B**, The pores occupy a large area of the cytoplasm. **C**, Sensitized mast cell fails to degranulate after challenge when pretreated with cromolyn sodium. (Courtesy Rhone-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pennsylvania.)

van der Wouden et al.⁷ found that most of the studies done had small samples that provided negative results; however, clinically relevant effects of sodium cromoglycate could not be excluded. What may be more telling is that the Global Initiative for Asthma (GINA) guidelines do not include cromolyn as an agent to be used in the treatment of asthma.⁴

Use for Cough Associated With Angiotensin-Converting Enzyme Inhibitor. Hargreaves and Benson⁸ reported that cromolyn sodium in a 5-mg MDI formulation, administered as two actuations four times daily, provided protection against the cough often seen as a side effect with use of angiotensin-converting enzyme (ACE) inhibitors.⁸ Cromolyn sodium significantly improved cough scores (frequency and severity) in 9 of the 10 patients in the study after 2 weeks. Cough was not completely suppressed in any of the 10 patients.

CLINICAL CONNECTION

Cromolyn sodium can assist in suppressing a cough associated with an angiotensin-converting enzyme (ACE) inhibitor.

Anti-Sickle Cell Effects. Both the intranasal solution and the 20-mg inhaled powder capsule of cromolyn given as a single dose were observed to cause a significant decrease in sickle cell percentage in nine African children with severe sickle cell disease. Improvement was seen 24 hours after administration of the single dose. The reduction in sickling is hypothesized to result from the blocking of calcium-activated potassium channels, which play a major part in water loss and erythrocyte dehydration.⁹

Clinical Application of Cromolyn Sodium

Three points should be emphasized about the clinical application of cromolyn sodium in asthma and hyperreactive airway states:

1. The drug is prophylactic only and should not be used during acute bronchospasm. This is based on its mechanism of action because the drug must already be present to prevent mast cell degranulation. *It has no bronchodilating action* and may cause further bronchial irritation as an aerosol.
2. Abrupt withdrawal of oral corticosteroids and substitution of cromolyn sodium in patients with asthma can result in inadequate adrenal function. Cromolyn has no effect on the adrenal system, and tapered withdrawal of corticosteroids is necessary while initiating cromolyn use in patients.
3. It may take 2 to 4 weeks for symptom improvement that enables a decrease in concomitant therapy, such as bronchodilator or steroid use.

Guidelines for the management of asthma indicate that cromolyn sodium is used in subjects requiring regular use of β agonists for control of symptoms. Use of cromolyn sodium is considered an alternative to the use of inhaled corticosteroids, especially in children.¹

Dosage Regulation. The protective effect of cromolyn in allergic, nonallergic, or reflex-induced asthma is dose dependent. The usual dosage of 20 mg four times daily (80 mg/day) with the nebulized solution in some cases can be reduced to a maintenance dosage of 40 to 60 mg/day after the patient's asthma remains stabilized for 1 or 2 months. Likewise, if the stimuli of asthma increase in severity (e.g., heavy exercise in cold weather [skiing] as opposed to walking in warm weather), higher dosages or addition of a β agonist may be required. For seasonal allergy, cromolyn should be started at least 1 week before allergen exposure. The drug is

protective if given 30 minutes before a specific allergen exposure (e.g., cat fur), and a single dose 15 minutes before exercise on an occasional, rather than a continuous, basis is effective. As stated previously, the degree of exercise and the conditions must be considered in estimating the protection required. Long-term continuous maintenance with cromolyn may be needed for patients with reflex-induced asthma or for patients with late-phase reactions or severe bronchial reactivity and lability.¹⁰

CLINICAL CONNECTION

Cromolyn is an alternative treatment for asthma in children. However, low-dose inhaled corticosteroids are preferred.

Antileukotriene Agents

The term *leukotriene* is based on the fact that these molecules were originally isolated from leukocytes, and the carbon backbone has three double bonds in series, termed a *triene*. Chemical structures of the three antileukotriene drugs currently available in the United States are shown in Fig. 12.5. Three antileukotriene agents (zafirlukast, montelukast, and pranlukast) attach to and block the receptor for **leukotrienes**; however, only zafirlukast and montelukast are approved for use in the United States. A fourth agent, zileuton, inhibits the synthesis of leukotrienes.

Leukotrienes and Inflammation

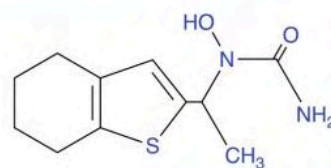
The **leukotrienes** are members of a group of biologically active fatty acids, including prostaglandins, thromboxanes, and lipoxins, that are known as *eicosanoids*. These molecules are lipid mediators of inflammation that are synthesized from the fatty acid precursor arachidonic acid (5,8,11,14-eicosatetraenoic acid). Arachidonic acid (AA) is found in cell nuclear membrane phospholipids. The leukotrienes mediate directly or indirectly at least some of the inflammatory process seen in asthma. They are potent bronchoconstrictors and stimulate other cells to cause airway edema, mucus secretion, ciliary beat inhibition, and recruitment of other inflammatory cells into the airway.¹¹

Cell Sources of Leukotrienes

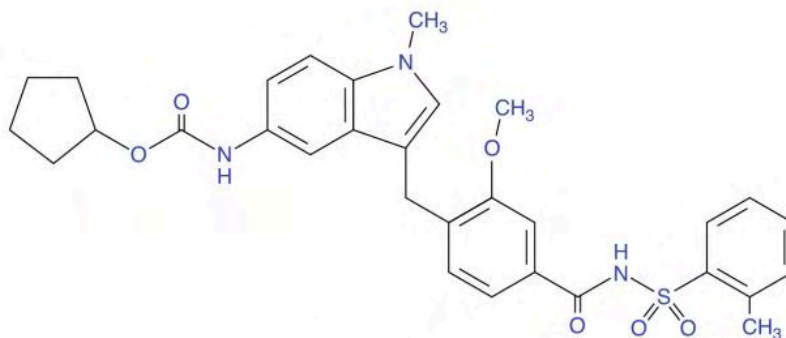
The leukotrienes and other lipid mediators are not preformed and stored in cells but, rather, are synthesized after a mechanical, chemical, or physical stimulus that activates phospholipase A₂ (PLA₂), an enzyme. These stimuli include antigen challenge of sensitized tissues and exposure to PAF or other cytokines. Certain cells, including eosinophils, mast cells, monocytes, macrophages, basophils, neutrophils, and B lymphocytes,¹² have the necessary enzymes to synthesize leukotrienes and other mediators. Eosinophils, mast cells, and macrophages are present and recruited to the lung in asthma.¹³

Biochemical Pathways

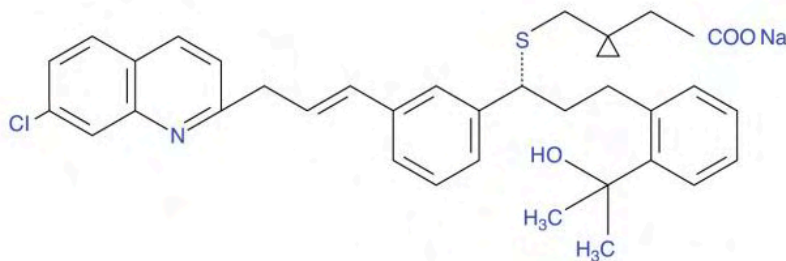
A simplified diagrammatic view of the AA cascade, which results in the various lipid mediators, is presented in Fig. 12.6. Essentially, free AA is converted to various lipid mediators by two routes: the cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways. The COX pathway results in the prostaglandins and thromboxane, and the 5-LO pathway results in the leukotrienes. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, inhibit the COX enzyme, blocking prostaglandin



Zileuton



Zafirlukast



Montelukast

• **Fig. 12.5** Chemical structures of the three antileukotriene agents: zileuton, zafirlukast, and montelukast.

and thromboxane production. There are two forms of the COX enzyme: COX-1 and COX-2. Many NSAIDs, such as aspirin, ketoprofen, and indomethacin, are mainly COX-1 selective; others, such as ibuprofen and naproxen, are slightly COX-1 selective. Some agents used to treat arthritis, such as celecoxib and rofecoxib, have primarily selective inhibition of COX-2. The 5-LO pathway results in the synthesis of leukotrienes; this pathway is the target for drugs in the antileukotriene group.

Leukotriene Production

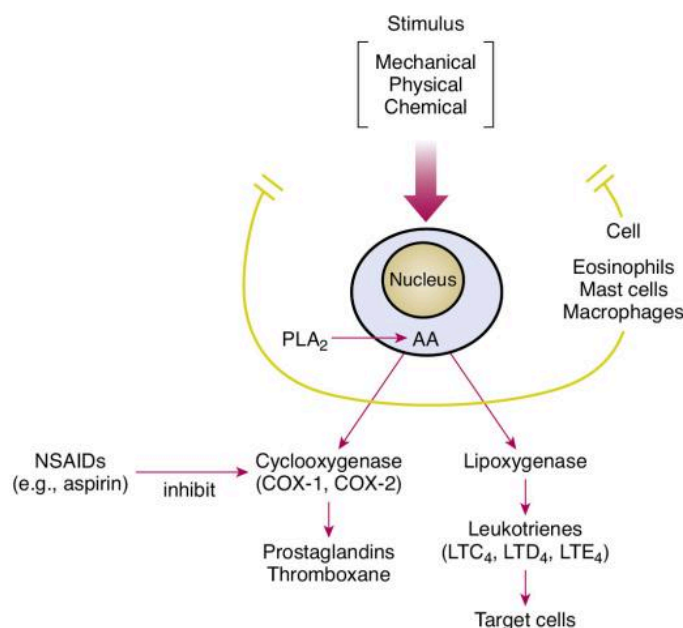
The lipoxygenase pathway resulting in leukotriene production is illustrated in Fig. 12.7. After stimulation of an appropriate cell, the enzyme PLA₂, which is located in the cell cytoplasm, moves to the cell nuclear membrane. In the nuclear membrane, PLA₂ hydrolyzes phospholipids to liberate free AA. AA binds to 5-LO-activating protein (FLAP) (AA-FLAP). Another enzyme, 5-LO, moves from both the nucleus and the cell cytoplasm to the nuclear membrane and interacts with the AA-FLAP complex to oxygenate the AA. This results in 5-hydroperoxyicosatetraenoic acid (5-HPETE), which is converted to the unstable intermediate leukotriene A₄ (LTA₄). LTA₄ is the source of all the other leukotrienes. LTA₄ is converted either into leukotriene B₄ (LTB₄) or the cysteinyl leukotriene C₄ (LTC₄). LTB₄ and LTC₄ are exported from the

cell to the extracellular space; LTC₄ is converted to leukotrienes D₄ and E₄ (LTD₄ and LTE₄). These three leukotrienes are termed *cysteinyl leukotrienes* (CysLTs) because they each have the amino acid cysteine in their chemical structure. The three CysLTs—LTC₄, LTD₄, and LTE₄—have been identified as the components of the previously termed *slow-reacting substance of anaphylaxis* (SRS-A).

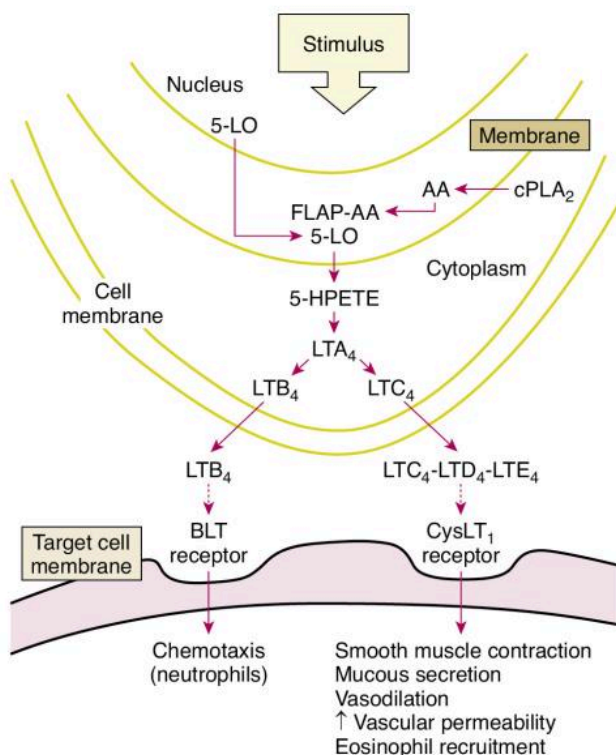
Cysteinyl Leukotriene Receptors and Effects of Leukotrienes

Leukotrienes bind to leukotriene receptors to exert their inflammatory effects. To date, several different receptor types have been identified. LTB₄ binds to a seven transmembrane-spanning receptor, termed the *B leukotriene (BLT) receptor*. The BLT receptor is involved in cellular recruitment (chemotaxis), probably of neutrophils, and may be involved in acute respiratory distress syndrome (ARDS).

CysLTs attach to two subtypes of receptors: CysLT₁ and CysLT₂ receptors. The proasthmatic actions of CysLTs are mediated by the CysLT₁ receptor, which is located on smooth muscle cells in the airway and other cell types. The human CysLT₁ receptor has been cloned and characterized.¹⁴ Stimulation of the CysLT₁ receptor causes bronchoconstriction, and CysLTs are more potent airway constrictors compared with histamine.¹⁵



• **Fig. 12.6** Simplified diagrammatic overview of stimuli and cell types involved in the arachidonic acid cascade, resulting in cyclooxygenase products, such as prostaglandins, and lipoxygenase products (the leukotrienes). AA, Arachidonic acid; COX-1, COX-2, isoenzyme forms of cyclooxygenase; LTC₄, LTD₄, LTE₄, leukotrienes C₄, D₄, E₄; NSAIDs, nonsteroidal antiinflammatory drugs; PLA₂, phospholipase A₂.



• **Fig. 12.7** Detailed model of synthesis of leukotrienes through the 5-lipoxygenase (5-LO) pathway and their effects on target cells. See text for a detailed description. AA, Arachidonic acid; BLT receptor, B leukotriene (LTB₄) receptor; cPLA₂, cytosolic phospholipase A₂; CysLT₁ receptor, cysteinyl leukotriene receptor subtype 1; FLAP, 5-lipoxygenase-activating protein; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; LTA₄, LTB₄, LTC₄, LTD₄, LTE₄, leukotrienes A₄, B₄, C₄, D₄, E₄.

In addition to direct bronchoconstriction, there is an increase in bronchial hyperresponsiveness to other irritants, such as histamine. Other effects include mucus secretion in the airway, increased vascular permeability causing airway wall edema, and plasma exudation into the airway lumen. The resulting protein and cellular debris in the airway, together with the mucus secretion, increases secretion viscosity and may lead to airway occlusion, such as that seen in asthma. CysLTs may also have an eosinophilic chemoattractant effect. Drugs that block the binding of leukotrienes to CysLT₁ receptors are named with the generic suffix *-lukast* (e.g., zafirlukast, montelukast, and pranlukast). The CysLT₂ receptor subtype mediates constriction of pulmonary vascular smooth muscle.¹⁵

CysLTs are produced largely by eosinophils, mast cells, and macrophages, all of which are cell types seen in the airways of patients with asthma. Elevated levels of CysLTs may be markers of asthma. Leukocytes of people with asthma release more CysLTs than the leukocytes of those who do not have asthma. Plasma levels of LTE₄ correlate with asthma severity and are elevated in urine during an asthma attack, during exercise-induced asthma, and in the presence of nocturnal asthma symptoms.¹³ Urinary LTE₄ levels are also elevated after challenge with an allergen in atopic asthma or with aspirin in aspirin-sensitive patients with asthma.¹¹

Zileuton (Zyflo)

Zileuton, available as Zyflo or Zyflo CR, is an orally active inhibitor of 5-LO. Its structure is shown in Fig. 12.5. This drug is indicated for prophylaxis and long-term treatment of asthma and is approved for use in adults and in children 12 years of age or older. It is considered a controller rather than a reliever and has no indication for use in an acute asthma episode.

Dosage and Administration

The dosage of zileuton is provided in Table 12.2. Zileuton is taken at mealtimes and at bedtime. Hepatic transaminase enzymes should be measured and evaluated before initiation of treatment, once a month for the first 3 months and every 2 to 3 months thereafter for the first year, with periodic monitoring for longer-term therapy. If clinical signs of liver injury (right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or flulike symptoms) develop, the drug should be discontinued.

Mechanism of Action

Taken orally, zileuton inhibits the 5-LO enzyme, which would otherwise catalyze the formation of leukotrienes from AA. Specifically, 5-LO in the presence of FLAP catalyzes the conversion of AA to the intermediate 5-HPETE, which is converted to LTA₄ and ultimately to other leukotrienes. By interrupting the synthesis of these biologically active leukotrienes, their contribution to the inflammatory responses in asthma is effectively blocked. Both the (R)-enantiomers and the (S)-enantiomers are active as 5-LO inhibitors. The mechanism of action of zileuton, along with those of other antileukotrienes, is illustrated in Fig. 12.8.

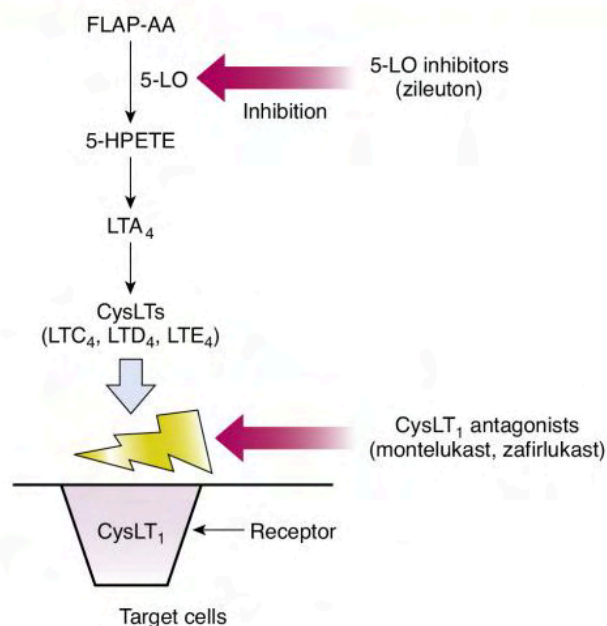
Pharmacokinetics

Zileuton is rapidly absorbed when taken orally, with an apparent volume of distribution of 1.2 L/kg. The drug is about 93% bound to plasma proteins, including albumin. The drug has a half-life of 2.5 hours, is metabolized to glucuronide conjugates and an *N*-dehydroxylated metabolite in the liver by cytochrome P450 enzymes, and is eliminated in urine and feces.

TABLE 12.2 Summary of Comparative Features of the Three Currently Available Antileukotriene Agents

	Zileuton (Zyflo)	Zafirlukast (Accolate)	Montelukast (Singulair)
Action	5-LO inhibitor	CysLT ₁ receptor block	CysLT ₁ receptor block
Age range	≥12 yr	≥5 yr	≥6 mo
Dosage	600-mg tablet qid or bid if extended release	10-mg or 20-mg tablet bid	Adult: 10-mg tablet every evening Children 6–14 yr: 5-mg tablet every evening Children 2–5 yr: 4-mg tablet every evening
Administration	Can be taken with food	1 hr before or 2 hr after meal	Taken with or without food
Drug interactions	Yes; theophylline, warfarin, propranolol	Yes; warfarin, theophylline, aspirin	No
Common side effects	Headache, dyspepsia, unspecified pain, liver enzyme elevations	Headache, infection, nausea, possible liver enzyme changes	Headache, flu-like symptoms, abdominal pain
Contraindications	Active liver disease or elevated liver enzymes; hypersensitivity to components	Hypersensitivity to components	Hypersensitivity to components

5-LO, Lipoxygenase; Bid, twice daily; CysLT₁, cysteinyl leukotriene receptor subtype 1; qid, four times daily.



• **Fig. 12.8** Illustration of the mechanism and site of action of the antileukotriene agents zileuton, zafirlukast, and montelukast. Zileuton inhibits the 5-lipoxygenase (5-LO) enzyme to prevent leukotriene production, and zafirlukast and montelukast antagonize the action of the cysteinyl leukotrienes (CysLTs) at the leukotriene receptor, CysLT₁. FLAP-AA, 5-Lipoxygenase-activating protein complexed with arachidonic acid; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; LTA₄, LTC₄, LTD₄, LTE₄, leukotrienes A₄, C₄, D₄, E₄.

Hazards and Side Effects

Side effects with oral zileuton are more severe than side effects with a placebo and include headache, general pain, abdominal pain, loss of strength, and dyspepsia. Elevations of one or more liver function test values with zileuton have been observed, and it is recommended that hepatic transaminases be monitored before and during treatment. Liver enzyme levels may decrease or return

to normal either during therapy or after discontinuation. Serum alanine transaminase (ALT), also known as *serum glutamate pyruvate transaminase (SGPT)*, is a good indicator of liver injury. Zileuton is contraindicated in subjects with acute liver disease or transaminase elevations greater than three times the upper limit of normal.

Zileuton interacts with two important drugs in respiratory care: theophylline and warfarin. Zileuton can increase serum theophylline concentrations and can increase prothrombin time when given concomitantly with warfarin. Dosage adjustments of theophylline and oral warfarin may be needed.

Zafirlukast (Accolate)

Zafirlukast (Accolate) is a synthetic asthma prophylactic agent (its structure is illustrated in Fig. 12.5). It is indicated for prophylaxis and long-term treatment of asthma and has been approved for use in children 5 years of age or older. This drug inhibits asthma reactions induced by exercise, cold air, allergens, and aspirin.

Dosage and Administration

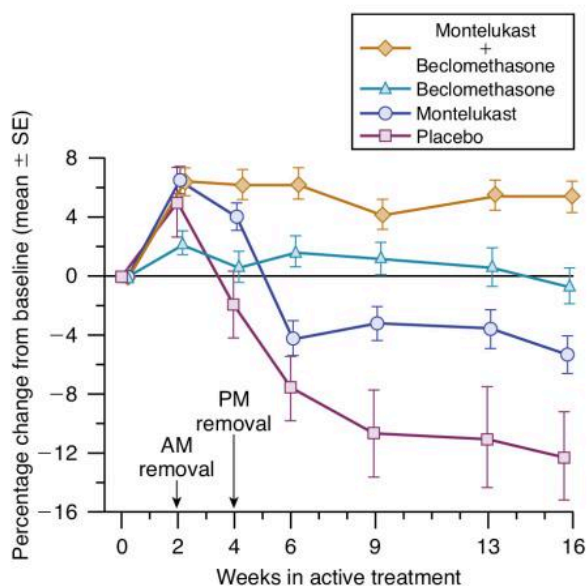
Dosage of zafirlukast can be found in Table 12.2. Zafirlukast's bioavailability can be reduced with the consumption of food; therefore it should be taken at least 1 hour before or 2 hours after eating.

Mechanism of Action

Zafirlukast and montelukast are both leukotriene receptor antagonists and block the inflammatory effects of leukotrienes (Fig. 12.9). Specifically, zafirlukast binds to the CysLT₁ receptors, with no agonist effect. This activity causes competitive inhibition of LTC₄, LTD₄, and LTE₄ and subsequent blockade of the inflammatory effects described previously in the section on leukotrienes and inflammation.

Pharmacokinetics

Zafirlukast is rapidly absorbed when taken orally. Peak plasma levels are reached 3 hours after administration, with an elimination



• **Fig. 12.9** Mean ($\pm$ standard error [SE]) percent change from baseline in four treatment groups receiving combined inhaled beclomethasone and oral montelukast, beclomethasone alone, montelukast alone, or a placebo. The a.m. and p.m. beclomethasone inhalers were replaced with a placebo in the montelukast and placebo groups during the run-in period. (From Lavolette, M., Malmstrom, K., Lu, S., et al. [1999]. Montelukast added to inhaled beclomethasone in treatment of asthma. *American Journal of Respiratory and Critical Care Medicine*, 160, 1862.)

half-life of approximately 10 hours. Zafirlukast is metabolized in the liver, with 10% excreted in the urine and the remainder excreted in feces. Administration of zafirlukast with food reduces mean bioavailability by about 40%.

Hazards and Side Effects

The most common side effects reported in healthy volunteers and patients were headache, infection, nausea, diarrhea, and generalized and abdominal pain. Respiratory infections were the predominant ones. Because zafirlukast is metabolized by liver enzymes, hepatic impairment (e.g., in cirrhosis) increases drug plasma levels. Although not noted in 6-month trials of zafirlukast, postmarketing surveillance indicated that doses greater than the 40-mg daily dose can cause elevations in serum aminotransferase concentrations.¹⁵ A case of hepatitis and hyperbilirubinemia with no other attributable cause has been reported in a patient receiving 40 mg/day for 100 days, indicating the possibility of liver enzyme dysfunction with the drug (this case was reported in the manufacturer's drug literature).

Montelukast (Singulair)

Montelukast (Singulair) is an orally active leukotriene receptor antagonist (its structure is illustrated in Fig. 12.5). It is indicated for prophylaxis and long-term treatment of asthma (as a controller) and has no bronchodilating effect for use in acute asthma treatment. Montelukast is also approved for allergic rhinitis. Montelukast is the only one of the three currently available antileukotriene agents that is approved for use in infants 6 months of age. Montelukast has been shown to have clinical efficacy in treating mild to moderate asthma and exercise-induced bronchoconstriction. Compared with a placebo, montelukast significantly improved

asthma control in children ages 12 to 23 months, children ages 2 to 14 years, adolescents ages 15 years or greater, and adults.^{16–20} To date, no safety issues with pediatric use have been reported. The manufacturer states that the drug has not been proven safe and effective in infants younger than 6 months of age. However, Knorr et al.²¹ found that the 4-mg dose of granules was just as safe and effective in infants ages 3 to 6 months as in children ages 6 to 24 months.

Dosage and Administration

The dosage of montelukast is provided in Table 12.2.

Montelukast can be taken with or without meals. Bioavailability when taken orally is not altered by a standard meal.

The oral granules can be directly poured into the mouth of the child or can be mixed with liquid or soft food. Infant formula, breast milk, applesauce, ice cream, and soft foods, such as carrots and rice, have been used in studies. The manufacturer also suggests that only these foods should be used.

Mechanism of Action

Similar to zafirlukast, montelukast is a competitive antagonist for the CysLTs LTC₄, LTD₄, and LTE₄. It binds with high affinity and selectivity to the CysLT₁ receptor subtype (see Fig. 12.8). Blockade of the CysLT₁ receptor prevents leukotriene stimulation of the receptor on target cells, such as airway smooth muscle and secretory glands. Montelukast has been shown to inhibit both early-phase and late-phase bronchoconstriction caused by antigen challenge.

Pharmacokinetics

Montelukast is rapidly absorbed after oral administration. With a 10-mg dose, peak plasma concentration occurs in 3 to 4 hours, with a mean oral bioavailability of 64%. This bioavailability has not been observed to be influenced by a standard meal in the morning. Concentration levels were slightly higher with the 5-mg chewable tablet taken while fasting in adults. For the 4-mg chewable tablet, the peak plasma concentration was reached in 2 hours. The drug is metabolized extensively in the liver and excreted in bile, with little urinary excretion. Mean plasma half-life in adults ranges from 2.7 to 5.5 hours. Mild to moderate hepatic insufficiency increases plasma levels, but no dosage adjustment is required. Severe hepatic impairment has not been evaluated.

Hazards and Side Effects

The safety profile of montelukast was similar to a placebo in drug testing. Adverse events that occurred in 2% or more cases included diarrhea, laryngitis, pharyngitis, nausea, otitis, sinusitis, and viral infection. Hypersensitivity reactions have been reported. Liver enzymes have not been observed to be altered compared with a placebo. Phenobarbital decreases the plasma level of montelukast, but the manufacturer suggests no dosage adjustment. If potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are used, appropriate clinical monitoring is suggested.

Role of Antileukotriene Drugs in Asthma Management

Antileukotriene agents are recommended in the NAEPP guidelines for the treatment of mild to moderate asthma.¹ Table 12.2 summarizes comparative features of the three currently available antileukotriene agents. Drazen et al.¹⁵ published an excellent review of asthma management with these agents.

CLINICAL CONNECTION

Antileukotriene agents are used as alternative treatment for asthma, but corticosteroids are preferred.

Protection Against Specific Asthma Triggers

Antileukotrienes are particularly useful in controlling asthma caused by certain triggers, including exercise-induced asthma, aspirin-induced asthma, and, to a lesser extent, allergen-induced asthma.^{15,22}

- **Exercise-induced asthma:** In exercise-induced asthma, cooling and drying of the airway promotes the generation of leukotrienes, resulting in bronchoconstriction. Although protection varies from complete to very little, the antileukotrienes develop no tolerance and may benefit patients who want to exercise or whose jobs require exercise under cold and dry conditions, without the use of short-acting rescue β agonists.
- **Aspirin-induced asthma:** In 3% to 8% of asthma cases, aspirin or NSAIDs can cause bronchoconstriction as a result of an increase in LTC₄ synthase activity. On the basis of such pathophysiology, which involves leukotriene production, leukotriene modifiers are the treatment of choice of patients with aspirin-induced asthma.
- **Allergen-induced asthma:** Antileukotrienes also block the early asthma response to allergen challenge and attenuate airway obstruction in the late-phase response. They are not completely effective in abolishing the late response that is also caused by histamine release.

Chronic Persistent Asthma

The evidence to date supports the use of antileukotriene agents in the management of mild, moderate, or severe chronic asthma.^{15,23,24} In mild to moderate asthma, antileukotrienes improve lung function, reduce the need for rescue β -agonist use, and decrease asthma symptoms, including nocturnal symptoms. In moderate to severe asthma, the additive effect between antileukotrienes and inhaled corticosteroids is the basis for asthma control with lower steroid doses or without an increase in steroid dosing (inhaled or oral). The advantages and disadvantages of antileukotriene drug therapy in asthma are summarized in [Box 12.3](#).

• BOX 12.3 Advantages and Disadvantages of Antileukotriene Drug Therapy in Managing Asthma

Advantages

- Oral administration, possible once-daily dosing
- Safe, with few side effects reported to date
- Effective in aspirin sensitivity and often in exercise-induced asthma
- Systemic distribution reaches entire lung through the circulation
- Additive effect with inhaled steroids
- May reduce steroid dose or prevent an increase in steroid dose
- Formulation approved for pediatric dosing (montelukast)

Disadvantages

- Antiinflammatory action limited to one mediator pathway
- Unknown long-term toxicity
- Variable response; effective in about 50% to 70% of patients
- No predictor to identify which patients will respond
- Systemic drug exposure, not limited to lung
- Generally not useful as monotherapy

Antileukotriene drug therapy is effective in approximately 50% of patients (although this proportion is greater for aspirin-sensitive individuals), but there is no method to predict which patients will be responders.^{25,26} Considerable intersubject variability in response has been seen. In a study of exercise challenge, 20 mg of zafirlukast gave complete protection in three subjects, partial protection in four subjects, and no protection in one subject.²⁷

Antileukotrienes in Relation to Corticosteroids

Asthma guidelines agree that corticosteroids are the most effective antiinflammatory drugs for use in asthma, and they have broader antiinflammatory activity compared with the more limited effect of antileukotrienes. Leukotriene modifiers affect only one biochemical pathway—the lipoxygenase path and resulting leukotriene effects. Two aspects of antileukotriene therapy should be considered in relation to the use of corticosteroids in asthma:

1. Choosing between an inhaled steroid and an antileukotriene in mild persistent asthma is based on offsetting advantages: the superior efficacy of inhaled steroids with possibly poor compliance versus the anticipated superior compliance of the orally administered antileukotrienes with their more limited antiinflammatory action.¹⁵
2. There is an additive effect with antileukotriene and inhaled corticosteroid therapies in mild to moderate asthma. A study by Laviolette et al.²⁸ showed a greater response to inhaled beclomethasone alone compared with oral montelukast alone; however, the combination of the two treatments resulted in the greatest improvement in lung function, as shown in [Fig. 12.9](#). In another study, use of montelukast by adults with asthma taking inhaled steroids long term resulted in a 47% reduction in steroid dose compared with a 30% reduction in the placebo group.²⁹

Churg-Strauss Syndrome

Churg-Strauss syndrome has been reported in a few patients treated with zafirlukast³⁰ or montelukast (postmarketing letter).³¹ Churg-Strauss syndrome is a vasculitis of unknown etiology, usually occurring in adults 20 to 40 years of age, marked by peripheral eosinophilia, eosinophilic infiltration of tissues, and necrotizing vasculitis that can result in major organ damage and death, if left untreated. The syndrome is rare, with a prevalence of about one case per 15,000 to 20,000 patient-years of treatment. To date, patients who developed this syndrome have had difficult-to-control asthma and have been taking oral or high doses of inhaled corticosteroids.

It is unclear whether the development of Churg-Strauss syndrome is an effect of antileukotriene treatment or whether the syndrome is unmasked by a reduction in corticosteroid therapy allowed by the antileukotriene therapy.¹⁵ In their review of eight patients, Wechsler et al.³¹ concluded that the occurrence of Churg-Strauss syndrome in patients with asthma receiving antileukotriene treatment seemed to result from the unmasking of an underlying vasculitic syndrome diagnosed as moderate to severe asthma and treated with corticosteroids. Nevertheless, experience in humans with antileukotriene drugs, specifically CysLT₁ receptor antagonists, is still new, and not all of the processes associated with 5-LO products are completely understood. For example, CysLT₂, which is *not* blocked by the CysLT₁ antagonists, such as zafirlukast or montelukast, has been identified on human pulmonary vasculature.¹³ The effect of introducing a potential imbalance with CysLT₁ antileukotriene therapy is not well understood. Although antileukotriene drugs seem to be safe and effective, additional clinical experience is needed.

Summary of Clinical Use of Antileukotriene Therapy

The following points summarize the current understanding of the role of antileukotriene drug therapy in asthma:

- Antileukotriene agents are prophylactic, controller drugs used in persistent asthma, including mild, moderate, and severe states; they are not indicated for acute relief or rescue therapy.
- Antileukotrienes can be tried as an alternative to inhaled corticosteroids or cromolyn-like agents in mild persistent asthma requiring more than as-needed β_2 agonists.
- Antileukotrienes may not be optimal as monotherapy in persistent asthma.
- Antileukotrienes may allow reduction of high-dose inhaled corticosteroids or prevent an increase in the dose of inhaled corticosteroids, and they reduce or prevent the need for oral corticosteroids.
- Evidence to date shows these agents are safe and often effective choices in managing a wide range of asthma severity.

Monoclonal Antibodies

CLINICAL CONNECTION

Monoclonal antibodies are used to treat severe asthma. These agents are valuable add-on treatments for patients with specific triggers.

Monoclonal antibodies are DNA-derived humanized IgG antibodies. Specifically, omalizumab blocks the attachment of IgE to mast cells reducing inflammatory mediators.³² Benralizumab, mepolizumab, and reslizumab block IL-5 in treating eosinophilic asthma.^{33–35} Dupilumab is a human IgG4 monoclonal antibody used to treat moderate to severe asthma in patients dependent on oral corticosteroids. Additionally, Dupixent (dupilumab) has been shown to reduce exacerbations in COPD patients. The newest monoclonal antibody is Trespire (tezepelumab-ekko) used to treat severe asthma by blocking a cytokine known as TSLP. In a systematic review it was noted that all the monoclonal antibodies discussed reduce the rate of asthma exacerbations and the use of oral corticosteroids.³⁶

Dosage and Administration

Monoclonal antibodies are agents that require injection or infusion. Dosing is every 2 or 4 weeks, depending on the agent. Recommended dosing is provided in Table 12.1. Refer to the manufacturer's package insert for specific dosing instructions.

Mechanism of Action

Omalizumab selectively binds to human IgE. The drug blocks the binding of IgE to the IgE receptor on the surface of mast cells and basophils (Fig. 12.10). This blocking allows reduction of mediators that can be released in an allergic response. Benralizumab, mepolizumab, and reslizumab block IL-5, changing the signaling of IL-5 reducing eosinophils. Dupilumab blocks IL-4 and IL-13, reducing inflammatory response.

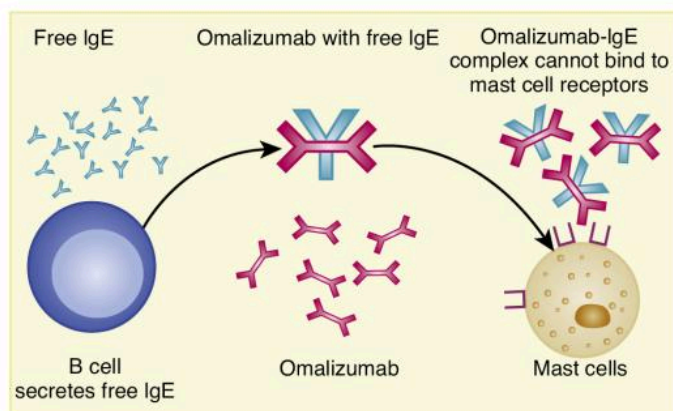
Hazards and Side Effects

The most severe reactions occurring in clinical trials with monoclonal antibodies were anaphylaxis. Other, more commonly observed reactions included injection site reactions, fever, headache, and sore throat.

Summary of Clinical Use of Monoclonal Antibodies

The following points summarize the current understanding of the role of monoclonal antibodies in asthma:

- Monoclonal antibodies are prophylactic agents used in uncontrolled severe persistent asthma; they are not indicated for acute relief or rescue therapy.



• **Fig. 12.10** Model of omalizumab complexing to free immunoglobulin E (IgE) to stop attachment to a mast cell, stopping mast cell degranulation. (Modified from Rosenwasser LJ, Nash DB. [2003]. Incorporating omalizumab into asthma treatment guidelines: consensus panel recommendations. *Pharmacy and Therapeutics*, 28, 400–414.)

- Monoclonal antibodies are not a replacement for inhaled corticosteroids.
- Monoclonal antibodies are not optimal as monotherapy in persistent asthma.
- Monoclonal antibodies may allow reduction of high-dose inhaled corticosteroids or prevent an increase in the dose of inhaled or oral corticosteroids.
- Monoclonal antibodies may allow reduction of asthmatic rescue agents.

RESPIRATORY CARE ASSESSMENT OF NONSTEROIDAL ANTI-ASTHMA AGENTS

Before Treatment

- Evaluate patient for optimal aerosol delivery formulation for inhaled medications, if more than one delivery system is available (e.g., small volume nebulizer [SVN] or MDI). Note age, ability to understand instructions, and need for reservoir with MDI.

During Treatment and Short Term

- Initially for aerosol medications: Instruct patient in use of aerosol delivery system selected (MDI, reservoir, SVN) and then verify correct use.
- Assess breathing rate and pattern.
- Assess breath sounds by auscultation before and after treatment.
- Assess pulse before and after treatment.
- Assess patient's subjective reaction to treatment for any change in breathing effort or pattern.
- Verify that patient understands that nonsteroidal antiasthma agents are controller drugs and understands their difference from a rescue bronchodilator (relieving agent); assess patient's understanding of the need for consistent use of these agents (compliance with therapy).
- Instruct patient in use of a peak flow meter to monitor baseline peak expiratory flow (PEF) and changes. Verify that there is a specific action plan based on symptoms and peak flow results. The patient should be clear on when to contact a physician with deterioration in PEF or exacerbation of symptoms.

Long Term

- Assess severity of symptoms (coughing, wheezing, nocturnal awakenings, and symptoms during exertion); use of rescue medication; number of exacerbations and missed work or school days; and pulmonary function. Modify level of asthma therapy (up or down, as described in NAEP Expert Panel Report 3 [EPR-3] guidelines for step therapy).
- Assess for presence of side effects with nonsteroidal antiasthma agents (refer to particular agent and its side effects, as listed previously).

General Contraindications

- In general, antiasthma agents are safe. However, each type of agent may affect each patient differently.
- Patients should understand that these agents are long-acting agents; if a crisis occurs, they should use short-acting medication.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify four nonsteroidal antiasthma drugs used in the management of chronic asthma; give generic and brand names.
2. Which immunoglobulin is implicated in allergy and is termed *cytophilic*?
3. Which type of asthma involves allergic reaction to an antigenic stimulus?
4. Which type of helper T cell, Th1 or Th2, is involved primarily in the atopic allergic response?
5. A resident wishes to order nebulized cromolyn sodium for a young patient with asthma in the emergency department who is wheezing and in moderate distress. Would you agree?
6. Which of the following could be recommended as possible choices for the patient with asthma in question 5: inhaled albuterol, inhaled salmeterol, inhaled ipratropium bromide, theophylline (either orally or intravenously)?
7. A patient with asthma has been taking 40 mg of oral prednisone for 1 week after an acute asthma attack and an emergency department visit. His physician now wants to switch him to inhaled cromolyn and discontinue the oral prednisone. What is the risk in doing this, and what would you recommend?
8. How does the mechanism of action of zafirlukast and montelukast differ from that of zileuton?
9. What is the recommended dosage and route of administration for zafirlukast, montelukast, and zileuton?
10. Which of the three antileukotriene agents in question 9 offers the most convenient dosing and the fewest drug interactions?
11. When would you recommend using omalizumab?
12. A 17-year-old patient with asthma has been treated for symptoms for the last 12 months. His symptoms have not improved despite the use of the highest dosage of an inhaled corticosteroid agent and regular use of salmeterol; in addition, trials on montelukast, cromolyn sodium, and oral theophylline have been unsuccessful. What would you recommend for this patient?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 45-year-old White woman is seen in the emergency department with a complaint of chest tightness, shortness of breath, and wheezing for the past 1.5 days. She also complains of a cough, with only occasional thin, whitish sputum during that period. She denies any fever or chills. She was diagnosed with adult-onset asthma 3 years ago and is sensitive to aspirin.

She has no history of tobacco use. She had a nasal polypectomy 2 years ago. She has been taking over-the-counter (OTC) racemic epinephrine for the past 4 months, as needed, because her albuterol prescription ran out. She was taking oral theophylline 300 mg twice daily from about 4 months ago. She is alert but mildly anxious.

Her vital signs are as follows: temperature (T) 97°F, pulse (P) 112 beats per minute, regular blood pressure (BP) 135/90 mm Hg, and respiratory rate (RR) 22 breaths per minute with no laboring. Expiration is slightly prolonged, but there is no use of accessory muscles. No cyanosis is evident. Auscultation reveals diffuse wheezes, greater on expiration than inspiration, and rhonchi bilaterally. Routine blood work later showed the following: hemoglobin at 13.5 g/dL and white blood cell (WBC) count at $6.1 \times 10^9/\text{mm}^3$, with 13% eosinophils. Electrolytes were also normal except for a plasma glucose level of 281 mg/dL. A chest radiograph showed some hyperinflation bilaterally, with no infiltrates, no pneumothorax, and normal heart size. Results of an arterial blood gas measurement on room air were pH 7.38, arterial carbon dioxide pressure (PaCO_2) 42 mm Hg, partial pressure of arterial oxygen (PaO_2) 72 mm Hg, base excess + 0.3 mEq/L, and arterial oxygen saturation (SaO_2) of 96%.

On questioning, the patient states that she has been using her OTC racemic epinephrine almost every 2 hours over the past 24 hours, with little improvement. She states that she has been experiencing many headaches, upset stomach, some lack of appetite, and insomnia often during the week. It has been 2 to 3 hours since she last used her OTC racemic epinephrine.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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13

Aerosolized Antiinfective Agents

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CHAPTER OUTLINE

Clinical Indications for Aerosolized Antiinfective Agents

Indication for Aerosolized Pentamidine
Indication for Aerosolized Ribavirin
Indication for Aerosolized Tobramycin
Indication for Aerosolized Aztreonam
Indication for Inhaled Zanamivir

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Respiratory Care Assessment of Aerosolized Antiinfective Agents

Before Treatment
During Treatment and Short Term
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Ribavirin
Tobramycin
Aztreonam
Zanamivir

Long Term
General Contraindications
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Aztreonam
Zanamivir

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to aerosolized antiinfective agents
2. Discuss the indications for inhaled antiinfective agents
3. List all available inhaled antiinfective agents used in respiratory therapy
4. Differentiate between specific antiinfective agent formulations
5. Discuss the route of administration available for the various antiinfective agents
6. Describe the mechanism of action for the various antiinfective agents
7. Recognize side effects for the various antiinfective agents
8. Discuss the use of each antiinfective agent in the treatment of lung disease

KEY TERMS AND DEFINITIONS

Cystic fibrosis (CF) Inherited disease of the exocrine glands affecting the pancreas, respiratory system, and apocrine glands. Symptoms usually begin in infancy and are characterized by increased electrolytes in the sweat, chronic respiratory infection, pancreatic insufficiency, and reduced fertility (females) and sterility (males).

Pneumocystis pneumonia (PCP) Interstitial plasma cell pneumonia caused by the organism *Pneumocystis jiroveci*. *Pneumocystis jiroveci* pneumonia (PJP) is common among patients with lowered immune system response.

Respiratory syncytial virus (RSV) Virus that causes formation of syncytial masses in infected cell structures.

Virostatic Stopping a virus from replicating.

Virucidal Killing a virus.

Virus Obligate intracellular parasite, containing either DNA or RNA, which reproduces by synthesis of subunits within the host cell and causes disease because of this replication.

This chapter discusses antiinfective agents currently approved for administration as inhaled aerosols: pentamidine isethionate (NebuPent), ribavirin (Virazole), tobramycin (TOBI), aztreonam (Cayston), and zanamivir (Relenza). Pentamidine is used to prevent and treat *Pneumocystis pneumonia (PCP)* in patients with acquired immunodeficiency syndrome (AIDS), and ribavirin is used to treat *respiratory syncytial virus (RSV)*. A single or monoclonal antibody preparation, palivizumab (Synagis), offers prophylaxis and treatment for RSV infection. Inhaled tobramycin and aztreonam are available for the management of *Pseudomonas aeruginosa* infections in patients with *cystic fibrosis (CF)*. Zanamivir is an inhaled antiviral agent used to treat influenza.

Clinical Indications for Aerosolized Antiinfective Agents

Clinical indications for each of the aerosolized antiinfective agents available at the time of this edition are given. Each agent is discussed separately in detail.

Indication for Aerosolized Pentamidine

Pentamidine by inhalation is indicated for the *prevention* of PJP in high-risk human immunodeficiency virus (HIV)-infected patients who have a history of one or more episodes of PCP or a peripheral CD4+ (T4 helper cell) lymphocyte count of 200/mm³ or less.

Indication for Aerosolized Ribavirin

Aerosolized ribavirin is indicated for the *treatment* of hospitalized infants with severe lower respiratory tract infection caused by RSV.

Indication for Aerosolized Tobramycin

Aerosolized tobramycin is indicated for the *management* (control) of chronic *P. aeruginosa* infection in CF.

Indication for Aerosolized Aztreonam

Aerosolized aztreonam is indicated to improve pulmonary symptoms in patients with CF and *P. aeruginosa* infection.

Indication for Inhaled Zanamivir

Inhaled zanamivir is indicated for the *treatment* of uncomplicated acute illness caused by the influenza virus in adults and children

who are 7 years of age and older and have been symptomatic for no more than 2 days. It may also be used prophylactically against the influenza virus in children 5 years of age and older.

Identification of Aerosolized Antiinfective Agents

The antiinfective agents available for inhalation are listed in Table 13.1 with details of formulation, usual recommended dosage, and clinical use. Each of these agents is discussed in more detail.

Aerosolized Pentamidine (NebuPent)

Pentamidine isethionate (NebuPent) is an antifungal agent that is active against *Pneumocystis jiroveci*, the causative organism for *Pneumocystis jiroveci* pneumonia (PJP). The chemical structure of pentamidine is shown in Fig. 13.1. Pentamidine can be given either parenterally or as an inhaled aerosol, but it is not absorbed with oral administration. When given parenterally, either intravenously or intramuscularly, the drug distributes quickly to the major organs (liver, kidneys, lung, and pancreas).

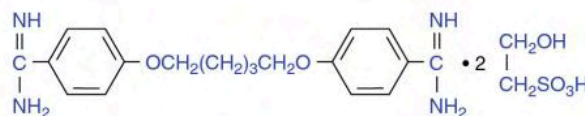
Introduction of Aerosolized Pentamidine

KEY POINT

Aerosolized pentamidine isethionate is approved for use as second-line prophylactic therapy in patients with acquired immunodeficiency syndrome (AIDS) to prevent *Pneumocystis pneumonia (PCP)*. Clinical experience with the aerosolized drug has resulted in significant side effects and less efficacy than with the oral agent trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX is indicated for prophylaxis of PCP unless side effects are not tolerated, in which case the aerosol drug should be considered.

CLINICAL CONNECTION

For administration of aerosolized pentamidine, a Respigard II nebulizer system should be used. Precautions should be taken against the spread of tuberculosis (TB) with patients with human immunodeficiency virus (HIV) infection, such as containment booths or isolation rooms. Patients with a history of lung disease should *not* use this agent in the aerosolized form.



• Fig. 13.1 Chemical structure of pentamidine isethionate (NebuPent).

TABLE 13.1 Currently Available Inhaled Antiinfective Agents With Formulations, Usual Recommended Dosage, and Clinical Use*

Drug	Brand Name	Formulation and Dosage	Clinical Use
Pentamidine isethionate	NebuPent	300 mg of powder in 6 mL of sterile water; 300 mg once every 4 wk	PCP prophylaxis
Ribavirin	Virazole	6 mg of powder in 300 mL of sterile water (20-mg/mL solution); given 12–18 hr/day for 3–7 days by SPAG-2 nebulizer	RSV
Tobramycin	TOBI; Bethkis; TOBI Podhaler; Kitabis Pak	TOBI: 300 mg/5 mL ampule Bethkis: 300 mg/4 mL ampule TOBI Podhaler: DPI: 28 mg/capsule Adults and children ≥6 yr: 300 mg bid, 28 days on/28 days off drug	<i>Pseudomonas aeruginosa</i> in CF
Aztreonam	Cayston	75 mg/1 mL Adults and children ≥7 yr: 75 mg tid, 28 days on/28 days off drug	<i>Pseudomonas aeruginosa</i> in CF
Zanamivir	Relenza	DPI: 5 mg/inhalation Adults and children ≥5 yr: 2 inhalations (one 5-mg blister per inhalation) bid <12 hr apart for 5 days	Influenza

*Details on use and administration should be obtained from manufacturer's drug insert material before use.

bid, Twice daily; CF, cystic fibrosis; DPI, dry powder inhaler; PCP, *Pneumocystis pneumonia*; RSV, respiratory syncytial virus; SPAG, small particle aerosol generator; tid, three times daily.

Both systemic administration and aerosol administration of pentamidine have been used for the treatment of PCP, which occurs as a common opportunistic respiratory infection in patients with AIDS. In addition to the prophylactic use of aerosolized pentamidine, the aerosol form has been used for the treatment of acute episodes. The first report by Montgomery et al.¹ was for therapy of acute episodes of PCP.

Rationale for Aerosol Administration

The rationale for aerosol administration of pentamidine to treat or prevent PCP is based on the same rationale for other inhaled aerosol drugs used to treat the pulmonary system: local targeted lung delivery, with fewer or less severe side effects compared with systemic administration. Aerosolized pentamidine produces significantly higher lung concentrations compared with intravenous administration.² The San Francisco prophylaxis trial showed that 300 mg of aerosolized pentamidine every 4 weeks was effective in preventing PCP in patients with HIV infection.³ Subsequent clinical experience with aerosolized pentamidine did not show improved clinical efficacy compared with oral drugs, such as TMP-SMX (Septra and Bactrim), and toxic side effects still occurred.

Description of *Pneumocystis Pneumonia*

The organism *Pneumocystis carinii* (now termed *Pneumocystis jiroveci*) was first noted in the lungs of guinea pigs by Chagas in 1909 and Carini in 1910. It was named as a new organism by Delanöe and Delanöe in 1912 as *Pneumocystis carinii* to describe the cystic form in the lungs and its earlier discoverer. Mammals are commonly infected with the organism at an early age, probably through an airborne vector. Disease occurs when there is suppression of the immune system. When not contained by a competent immune system, *P. jiroveci* causes PCP. Before the AIDS pandemic, PCP was reported in malnourished infants in the 1940s and 1950s and in the 1970s in premature infants who survived.⁴ PCP produces a foamy intraalveolar exudate that contains cysts of *P. jiroveci*. The life cycle of *P. jiroveci* and the resulting pneumonia are illustrated in Fig. 13.2.

Conflicting names for *P. carinii* may be found in the literature. Stringer et al.⁵ described that the name was changed to

Pneumocystis jiroveci in honor of Otto Jírovec, a Czech parasitologist. However, in a letter to the editor, Hughes⁶ pointed out that the name change is not valid or final because it has not been registered in the International Code of Botanical Nomenclature. Hughes⁶ also pointed out that the name change would cause confusion in discussions of *P. carinii* because many clinicians still use this name. In a letter, Gigliotti⁷ supported the stance taken by Hughes that no clear evidence exists for the occurrence of an official name change.

What is known is that *P. carinii*, or *P. jiroveci*, is a fungus. The acronym PCP for *Pneumocystis pneumonia* remains the same⁵; however, most authors utilize the term PJP.

Dosage and Administration

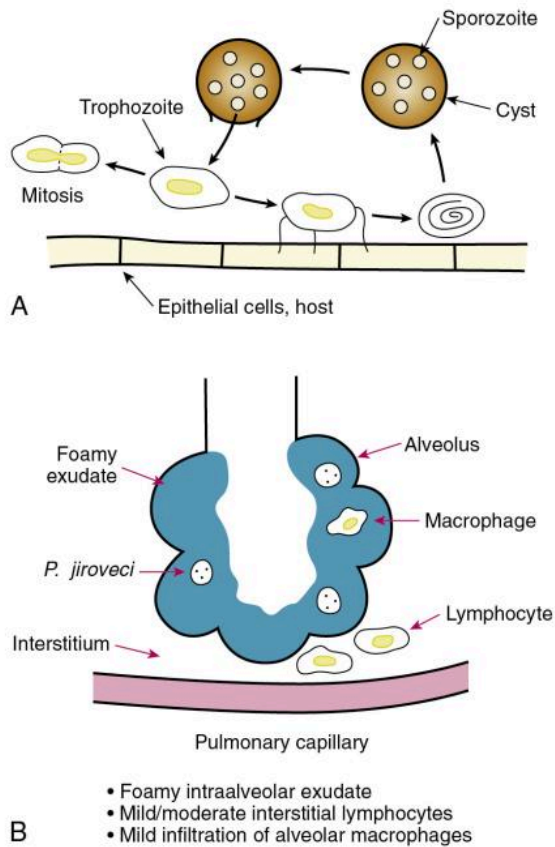
Details of dose and administration of NebuPent, the aerosolized brand name of pentamidine, can be found in the manufacturer's literature. The following summary is not intended to replace the more detailed instructions that accompany the drug.

Dosage. The approved dose of aerosolized pentamidine (NebuPent) for prophylaxis of PJP in patients with AIDS is 300 mg given by inhalation once every 4 weeks. This dose may be altered by physicians in treating individual patients.

NebuPent is supplied as a dry powder with 300 mg in a single vial. This powder must be reconstituted with 6 mL of sterile water for injection, United States Pharmacopeia (USP) (not saline, which can cause precipitation), added to the vial. The entire 6 mL of reconstituted solution is placed into a nebulizer.

Administration. Approval of aerosolized pentamidine by the US Food and Drug Administration (FDA) was for administration with the Respirgard II nebulizer (Vital Signs, Inc., Totowa, New Jersey). This is a small volume nebulizer (SVN) system, powered by compressed gas, fitted with a series of one-way valves and an expiratory filter (Fig. 13.3). This nebulizer system has been described by Montgomery and associates.² The Respirgard II nebulizer should be powered with a flow rate of 5 to 7 L/min from a 50-pounds per square inch (psi) source or, alternatively, by controlling the flow with a 22- to 25-psi pressure source connected to the small-bore tubing of the nebulizer. Pressures below 20 psi are insufficient to produce the desired particle size necessary for

peripheral delivery of the drug. These requirements with Respirgard II are found in the manufacturer's literature and discussed further by Corkery et al.⁸ It may also be noted that pentamidine may also be administered in a room or tent that acts as a "vacuum"



• **Fig. 13.2** Pathogenesis of *Pneumocystis jiroveci*, the organism that causes *Pneumocystis pneumonia* (PCP). **A**, Life cycle of *P. jiroveci*. **B**, PCP pathology.

to draw any particles that have escaped to a filter. Capturing of these particles results in less exposure to the respiratory therapist.

Nebulizer Performance. Although nebulized pentamidine was approved for general clinical use with the Respirgard II nebulizer system, other nebulizers have been used to administer the drug. At present, the manufacturer recommends use with a Respirgard II nebulizer system.

The general requirement for effective nebulization of pentamidine is a particle size or distribution of sizes with a mass median diameter (MMD) of 1 to 2 μm . This particle size is needed for the following two reasons⁵:

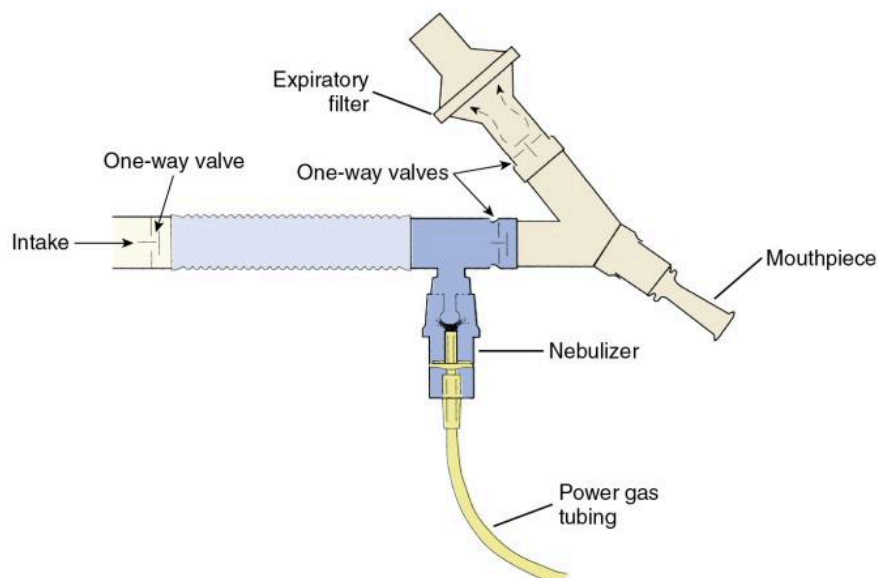
1. To achieve peripheral intraalveolar deposition targeted at the location of the microorganism
2. To reduce or prevent airway irritation seen with larger particle sizes, which deposit more in larger airways

Studies by Vinciguerra and Smaldone⁹ and by Smaldone et al.¹⁰ have examined nebulizer performance and compared treatment time and patient tolerance of aerosolized pentamidine with Respirgard II versus other nebulizers. Treatment times and efficiency in drug availability were greater with the AeroTech II (CIS-US, Bedford, Massachusetts) compared with the approved Respirgard II.

Mechanism of Action

The exact mechanism of action of pentamidine is unknown. The toxic effect of the drug on *P. jiroveci* may result from multiple actions. Pentamidine blocks RNA and DNA synthesis, inhibits oxidative phosphorylation, and interferes with folate transformation.^{4,11,12}

When given by inhaled aerosol, pentamidine reaches significantly higher concentrations in the lung than when given intravenously.² The inhaled drug first binds to lung tissue. Although plasma levels are much less than with parenteral administration, the drug is slowly absorbed into the circulation and distributed to body tissues, as with parenteral administration. As a result, prolonged aerosol administration can result in systemic accumulation. Approximately 75% of the drug is excreted in urine and 25% in feces over the months after administration.



• **Fig. 13.3** Diagrammatic illustration of Respirgard II nebulizer system, showing one-way valves and expiratory filter to scavenge exhaust aerosol.

Side Effects

The side effects seen with systemic therapy of PCP with use of either pentamidine or TMP-SMX have provided part of the rationale for aerosol administration of pentamidine. Although both of these drugs are effective in most patients with PCP when given systemically, greater than 50% of patients experience adverse side effects.

Side Effects With Parenteral Pentamidine. Side effects with parenteral administration of pentamidine have been summarized in several reviews, with numerous references.^{8,11} Parenteral use of pentamidine has resulted in the following:

- Pain, swelling, and abscess formation at the site of injection with intramuscular administration
- Thrombophlebitis and urticarial eruptions with intravenous administration
- Hypoglycemia (up to 62% of patients), with a cumulative cytotoxic effect on pancreatic beta cells
- Impaired renal function and azotemia
- Hypotension
- Leukopenia
- Hepatic dysfunction

Side Effects With Aerosol Administration. Side effects with aerosol administration can be differentiated into local airway effects and systemic effects. Local airway effects with aerosol administration have included the following:

- Cough and bronchial irritation in 36% of patients in one study³
- Shortness of breath
- Bad taste (bitter or burning) from the aerosol impacting in the oropharynx
- Bronchospasm and wheezing in 11% of patients³
- Spontaneous pneumothoraces¹³

In addition, the following *systemic reactions* have occurred with aerosolized pentamidine:

- Conjunctivitis
- Rash
- Neutropenia
- Pancreatitis¹⁴
- Renal insufficiency
- Dysglycemia (hypoglycemia and diabetes)
- Digital necrosis in both feet¹⁵
- Appearance of extrapulmonary *P. jiroveci* infection

Because of the pharmacokinetics of pentamidine, long-term treatment with the aerosol can lead to tissue accumulation in the body, causing some of the same side effects as with parenteral administration. Suppression of *P. jiroveci* with local targeting of the lung has resulted in the appearance of infection elsewhere in the body.

Preventing Airway Effects. Use of a β -adrenergic bronchodilator before inhaling aerosolized pentamidine can reduce or prevent local airway reaction, including reduction of coughing or wheezing. Ipratropium has also been shown by Quieffin et al.¹⁶ to prevent bronchoconstriction. The airway reaction may be caused by the sulfite moiety in isethionate (see Fig. 13.1), which is known to cause airway irritation, or by the drug itself.^{17,18} This effect can be reduced by use of a nebulizing system producing very small particle sizes, which lessen airway deposition and increase alveolar targeting.⁸

Environmental Contamination by Nebulized Pentamidine

The following concerns exist regarding environmental contamination from nebulized pentamidine:

- Exposure to the drug itself from the exhaust aerosol
- Risk of infection with tuberculosis (TB), a disease associated with AIDS, from patients being treated with aerosolized pentamidine

Pentamidine is not known to be teratogenic, based on its use in pregnant women with African sleeping sickness (trypanosomiasis), although detailed clinical data were not kept. The drug is not mutagenic, and its carcinogenic potential is considered minimal.¹¹ Studies have shown that low levels of pentamidine can be detected in health care workers exposed to the drug during treatments.^{19,20} The investigators concluded that exposure probably occurred during treatment interruptions, usually caused by coughing episodes. Health care workers have also complained of conjunctivitis and bronchospasm when aerosolizing the drug.¹¹ On the basis of these reports and the long tissue half-life of pentamidine, contact with the drug should be kept to a minimum or avoided, if possible.

The risk of contracting TB when treating patients with AIDS with nebulized pentamidine is based on the association of TB and AIDS, the airborne mode of transmission of TB, and the fact that pentamidine aerosol can cause coughing and expulsion of droplet nuclei containing TB bacilli during aerosol treatments.

Environmental Precautions. The following precautionary measures are suggested when administering aerosolized pentamidine to reduce the risk of drug exposure and TB infection^{21–24}:

- Use a nebulizer system with one-way valves and an expiratory filter.
- Stop nebulization if the patient takes the mouthpiece out of the mouth (a thumb control on the power gas tubing gives more control).
- Use nebulizers producing an MMD of 1 to 2 μm to increase alveolar targeting and lessen large airway deposition and cough production.
- Always use a suitable expiratory filter and one-way valves with the nebulizer. Instruct patients to turn off the nebulizer when talking or when taking it out of the mouth.
- Screen patients for cough history and pretreat with a β agonist, with sufficient lead time for effect in reducing the bronchial reactivity.
- Administer aerosol in a negative-pressure room, with six air changes per hour, or consider using an isolation booth/hood assembly with an exhaust fan and air directed through a high-efficiency filter.
- Health care workers should use barrier protection (gloves, mask, and eyewear).
- Screen patients with HIV infection for TB, and treat where evidence of infection exists.
- Do not allow treatment patients to interact with others until coughing subsides.
- Health care workers should periodically screen themselves for TB.
- Pregnant women and nursing mothers should avoid exposure to the drug, and all practitioners should limit exposure to the extent possible.

Although measures exist to radically limit environmental contamination with aerosolized pentamidine, many of these are expensive, such as negative-pressure rooms and improved ventilation exchange in older buildings. Other measures are difficult, such as the wearing of effective high-efficiency masks in a busy clinical setting for a prolonged period. The use of room disinfection with ultraviolet light has been reviewed²⁵ but is debated.²²

CLINICAL CONNECTION

Aerosolized pentamidine is *only* used in prophylaxis. Trimethoprim-sulfamethoxazole (TMP-SMX) is used to treat active *Pneumocystis pneumonia* (PCP).

Aerosol Therapy for Prophylaxis of Pneumocystis Pneumonia: Clinical Application

Comparisons of the efficacy of aerosolized pentamidine with oral TMP-SMX, together with reports of serious adverse effects with aerosolized pentamidine, led to a reevaluation of aerosol therapy with pentamidine for prophylaxis of PCP. General recommendations for prophylaxis of PCP have been published by the US Centers for Disease Control and Prevention (CDC) in *MMWR Recommendations and Reports* for HIV-positive children²⁶ and guidelines for adults.²⁷ In the 2018 CDC recommendations, oral TMP-SMX is preferred for treatment and prophylaxis of PCP as long as adverse side effects from TMP-SMX were absent or acceptable.²⁷ Aerosolized pentamidine is recommended as an alternative therapy for primary and secondary prophylaxis of PCP; it is not recommended as a treatment.²⁷

Ribavirin (Virazole)

KEY POINT

Ribavirin is an aerosolized antiviral drug used to treat respiratory syncytial viral (RSV) infection in children and infants at risk for severe or complicated disease.

CLINICAL CONNECTION

Ribavirin is administered with a small-particle aerosol generator, model 2 (SPAG-2) unit. Side effects with ribavirin include pulmonary deterioration and equipment malfunction (ventilator occlusion and endotracheal tube occlusion). Environmental containment systems are available to protect caregivers.

Ribavirin (Virazole) is classified as an antiviral drug; it is active against RSV, influenza viruses, and herpes simplex virus. Chemically, it is a nucleoside analog and resembles guanosine and inosine.²⁸ Ribavirin is **virostatic**, not **virucidal**, and inhibits DNA and RNA (retrovirus) viruses.

Ribavirin has been used throughout the world for various viral infections, including RSV and influenza types A and B. Clinical trials of aerosolized ribavirin for severe RSV infection conducted by Hall et al.²⁹ have shown significant improvement with ribavirin treatment compared with a placebo; however, Guerguerian et al.³⁰ have noted its ineffectiveness.

Clinical Use

Infection with RSV in children results in either bronchiolitis or pneumonia. Guidelines concerning the use of ribavirin were published by the Committee on Infectious Diseases of the American Academy of Pediatrics in 2018. Generally, the drug is not recommended for routine RSV infection, but it may be considered for treating life-threatening infections.³¹ The Agency for Healthcare Research and Quality (AHRQ) has designated ribavirin as “possibly ineffective.”³²

Ribavirin treatment by aerosol is expensive and risks environmental exposure to the drug by personnel. Studies have given conflicting results on whether the use of ribavirin significantly reduces

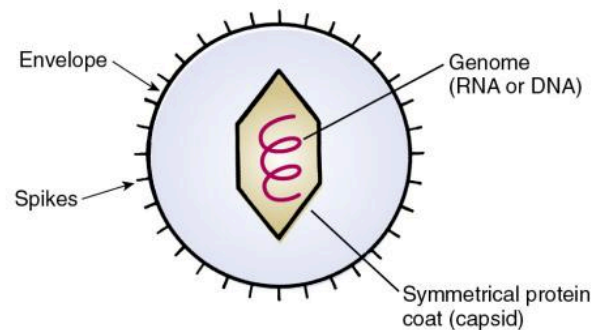
outcomes, such as ventilator days, oxygen needs, intensive care unit days, hospital days, or mortality.^{33,34}

Nature of Viral Infection

A summary of viruses and viral infection is presented to establish key principles and concepts needed for understanding the difficulties in treating viral diseases and the mechanism of action of ribavirin. A **virus** can be defined as an obligate intracellular parasite, containing either DNA or RNA, which reproduces by synthesis of subunits within the host cell and causes disease because of this replication.

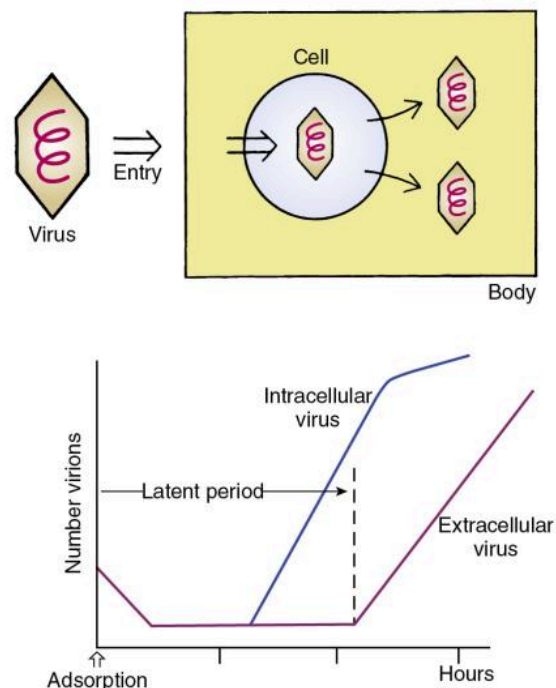
Fig. 13.4 illustrates the simple structure of a virus. These are primitive members of the animal kingdom, submicronic in size, that consist of a strand of DNA or RNA that is surrounded by a protein coat. A virus may or may not be surrounded by an envelope, whose glycoprotein spikes are partially obtained from the host cell.

The concept and sequence of a viral infection are shown in Fig. 13.5. A virus enters the body through various routes (oral, inhaled, mucous membranes) and invades a host cell. This is a



Virion: extracellular virus particle

• **Fig. 13.4** Structure of a virus, showing nuclear material (DNA or RNA), protein coat, and envelope.



• **Fig. 13.5** Sequence of viral infection, illustrating intracellular replication before dissemination in the body.

multistep process consisting of phases in which the virus adsorbs to the cell; penetrates the cell; uncoats itself; goes through a process of recoding cell DNA (transcription, translation, synthesis); assembles itself; and sheds from the cell. The host cell usually dies in the process. Clinically, signs of a viral infection do not occur until after the initial latent period, when the virus leaves the cell (see Fig. 13.5). At this point, infection is well established. The diagnosis of viral illness is usually based on clinical signs, including the symptoms, age of the patient, and time of year. Definitive diagnosis requires isolating the virus or showing an antibody titer increase. Diseases produced by viruses include chickenpox, smallpox, fever blisters (herpes simplex virus), genital herpes, poliomyelitis, the common cold, AIDS, influenza, mumps, and measles.

Because of the nature of viral infection, as just outlined, antiviral drug treatment, whether for the common cold or for HIV infection, is difficult. In particular, there are three complications in treating viral disease with drugs, as follows:

1. Attacking the intracellular virus may harm the host cell.
2. Viral replication is maximal before the appearance of symptoms.
3. Viruses have the property of antigenic mutability; that is, they change their appearance to the immune system.

Respiratory Syncytial Virus Infection. RSV can cause bronchiolitis and pneumonia. Almost all children are exposed to RSV by the second year of life, and in most the infection is mild and self-limiting. Outbreaks of RSV pneumonia are seasonal and peak during winter months (November to March), with some variation according to geographic region.

The name of the virus reflects its effects on cells, which is to cause the formation of large, multinucleated cells, or a *syncytium*. The virus spreads easily via personal contact or hand contamination from surfaces. No effective vaccine exists to prevent RSV respiratory disease. Prepared antibody to RSV is available and is discussed later in the chapter.

Dosage and Administration

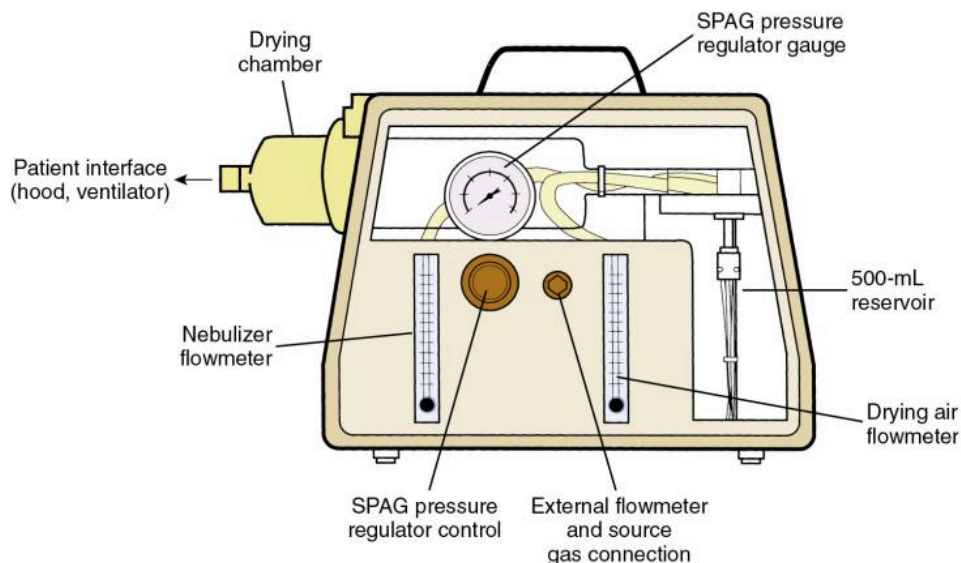
Following is a summary of ribavirin dosage and administration. It is not intended to replace detailed instructions contained in the manufacturer's literature, which should be reviewed before

administering this drug. This includes the operating manual for the small-particle aerosol generator, model 2 (SPAG-2) nebulizing system.

Dosage. Ribavirin is given as a 20-mg/mL solution, which is administered by nebulizer (SPAG-2) for 12 to 18 hours per day, for a minimum of 3 days and not greater than 7 days. The drug is supplied as 6 g of powder in a 100-mL vial. The powder is reconstituted in the vial with sterile water for injection or inhalation, transferred to the large volume (500-mL) reservoir of the nebulizer, and diluted further to a total volume of 300 mL with sterile water. This gives a concentration of 6 g/300 mL, or 20 mg/mL, a 2% strength solution.

Administration. Clinical trials of ribavirin aerosol were carried out with a large-volume nebulizing system, the SPAG-2. The drug was approved for general use with this aerosol generator. A diagram of the SPAG-2 unit is shown in Fig. 13.6. It is a large-volume, pneumatically powered nebulizer operating on a jet shearing principle, with baffling of aerosol particles and a drying chamber to reduce particle size further to a level of approximately 1.3 μm MMD. Solutions in the SPAG-2 reservoir should be replaced after 24 hours. Residual solution in the reservoir should be discarded before adding newly reconstituted solution. The drug solution should always be visually inspected for particulate matter or discoloration before use.

The nebulizer is connected to a hood as the patient interface. The manufacturer specifically warns against administration of the drug to infants requiring mechanical ventilation because of the risk of drug precipitation occluding expiratory valves and sensors or the endotracheal tube. The sickest infants with RSV are likely to need ventilatory support; however, there are reports of drug use with mechanical ventilation. Demers et al.³⁵ provided detailed information concerning precautions with ventilator use during administration of the drug. A clinical study of aerosol administration with mechanical ventilation of infants with severe RSV infection was reported by Smith et al.³³; these authors showed that treatment reduced duration of ventilation, oxygen support, and hospital stay. Although labor intensive, mechanical ventilatory administration of ribavirin simplifies environmental control.



• **Fig. 13.6** Diagrammatic illustration of small particle aerosol generator (SPAG-2) unit used for nebulizing ribavirin.

Ribavirin has used the SPAG and been FDA cleared for use; however, new forms of aerosol generation have continued. Walsh and Liu³⁶ utilized a vibrating mesh nebulizer to deliver ribavirin and found that the nebulizer did not affect the properties of ribavirin.

Mechanism of Action

The mechanism of action by which ribavirin exerts its virostatic effect is not completely understood. Viral inhibition is probably based on its structural resemblance to the nucleosides used to construct the DNA chain.²⁸ Fig. 13.7 shows the structures of the natural nucleoside guanosine with ribavirin, which is a synthetic nucleoside analog. During the formation and assembly of new viral protein within the cell, ribavirin is most likely taken up instead of the natural nucleoside to form the DNA chain; this prevents construction of viable viral particles and subsequent shedding of virus into the bloodstream. Fig. 13.8 is a conceptual illustration of the process. Ribavirin does not prevent the attachment or the penetration of RSV into the cell, which may explain why it merely reduces the severity of illness rather than preventing or abolishing it altogether.²⁸

When given via inhaled aerosol, ribavirin levels are much greater in respiratory secretions than in the bloodstream. Waskin¹¹ provided a referenced summary of ribavirin kinetics. With 8 to 20 hours of aerosol treatment, peak plasma levels are 1 to 3 mcg/mL, and respiratory secretion levels are greater than 1000 mcg/mL. The minimal inhibitory concentration (MIC) for RSV is 4 to 16 mcg/mL. The half-life of ribavirin is about 9 hours in plasma and about 1 to 2 hours in respiratory secretions, which is the rationale for almost-continuous administration via aerosol.

Side Effects

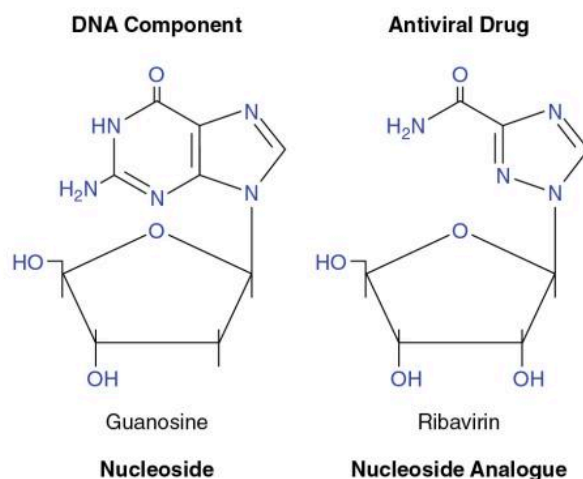
Side effects seen with aerosolized ribavirin are listed in the product literature and have been reviewed by Waskin.¹¹ The following list summarizes adverse effects reported, including those seen in adults receiving the drug:

- **Pulmonary:** Deterioration of pulmonary function and worsening of asthma or chronic obstructive pulmonary disease

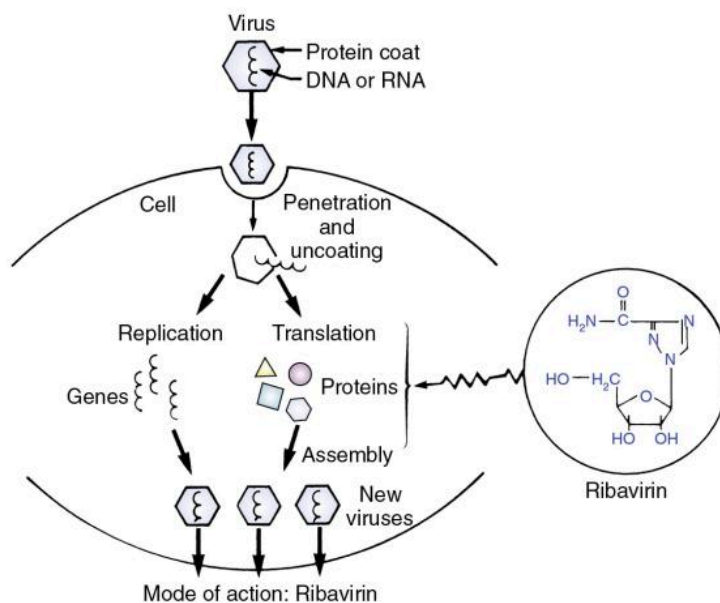
(COPD) occur; pneumothorax, apnea, and bacterial pneumonia have been described.

- **Cardiovascular:** Cardiovascular instability, including hypotension, cardiac arrest, and digitalis toxicity, has been noted.
- **Hematologic:** Effects on blood cells have been reported with oral or parenteral administration but not with aerosol use. Reticulocytosis (excess of young erythrocytes in the circulation) has been reported with aerosol use.
- **Dermatologic/topical:** Rash, eyelid erythema, and conjunctivitis have been noted.
- **Equipment-related:** Equipment-related adverse effects with ribavirin treatment include occlusion and impairment of expiratory valves and sensors with ventilator use and endotracheal tube blockage from drug precipitate.

Although all of the previously listed effects have been reported, common effects clinically are pulmonary function deterioration,



• **Fig. 13.7** Similarity of the ribavirin molecule to guanosine, the DNA precursor component, may be the basis for the virostatic effect of the drug.



• **Fig. 13.8** Illustration of mechanism of action of ribavirin in blocking viral replication.

equipment malfunction caused by drug precipitate, and skin irritation resulting from excess drug precipitation.

Environmental Contamination With Aerosolized Ribavirin

There is concern among health care workers over exposure to ribavirin. The drug has potential for mutagenic and carcinogenic effects, as indicated by in vitro and animal studies.¹¹ The effect on fertility is uncertain, but the drug has caused testicular lesions in rats. The effect on pregnancy is of concern because the drug is teratogenic or embryocidal in animal species. Acute effects from aerosolized ribavirin reported by health care workers have included precipitation on contact lenses and conjunctivitis, headache (51%), rhinitis, nausea, rash, dizziness, pharyngitis, and lacrimation (10%–20%). Several cases of bronchospasm or chest pain have been reported by individuals with reactive airways disease. The symptoms noted have resolved within hours after discontinuing exposure to the drug.³⁷

Minimal levels of ribavirin exposure are difficult to specify because of the lack of dose–response data for humans.³⁸ Corkery et al.³⁹ stated that the California Department of Health Services recommended an acceptable occupational airborne concentration for 8 hours of limited exposure to be $\frac{1}{1000}$ of the lowest no-observed-effect level, which would be 2.5 mcg/m³.

Although there are no reports, to date, of serious effects from drug exposure via aerosol, precautions to limit or avoid exposure to the drug are well indicated, as advocated by Kacmarek.⁴⁰ Pregnant females, or those wishing to become pregnant, should avoid exposure to the drug, if possible. In addition, environmental containment is superior to personnel barrier protection alone. Standard surgical masks do not prevent inhalation of 1- to 2- μ m particles. Dermal absorption of ribavirin seems to be negligible.⁴¹ It may be helpful to use a containment system when the drug is aerosolized to an oxygen hood; several systems have been proposed in the literature.^{42–44} All have common features of enclosure around the hood, with vacuum extraction and filtering of gas from the enclosure. Details needed for use can be found in the references given. It is recommended that the drug be administered in well-ventilated areas—that is, six or more air changes per hour.

Palivizumab (Synagis)

Palivizumab (Synagis) is an F protein inhibitor monoclonal antibody.⁴⁵ The drug is approved for the prevention of RSV in pediatric patients.

Clinical Use

Palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children. Safety and efficacy were established for infants with bronchopulmonary dysplasia (BPD), infants born prematurely (<35 weeks), and children with congenital heart disease.⁴⁶

Dosage and Administration

The powder for injection is lyophilized or freeze dried and is available at 50 or 100 mg/mL. A premixed injection of 100 mg/mL is also available. The recommended dose is 15 mg/kg given intramuscularly once a month before the start of and throughout the RSV season.

Mechanism of Action

Palivizumab is a humanized monoclonal antibody produced by recombinant DNA techniques, directed against the F protein of

RSV. As an antibody against RSV, palivizumab provides neutralizing and fusion-inhibiting activity, preventing viral replication.

Adverse Reactions

The most serious adverse reaction is anaphylaxis; however, this occurs in less than 1 per 100,000 cases. Other reactions that occurred in treatment and placebo groups included fever, upper respiratory infection, otitis media, rhinitis, rash, pain, hernia, and coughing and wheezing.³⁷

Clinical Efficacy

In a large multicenter trial of infants at high risk of RSV infection, palivizumab given intravenously at 15 mg/kg reduced the rate of hospitalization resulting from RSV infection to 4.8% compared with 10.6% in placebo recipients.⁴⁷ Adverse events were similar in placebo and treatment groups.

Feltes et al.⁴⁸ found that palivizumab is safe and effective for RSV-positive children with congenital heart disease. In this study, 53% of the children had reduced hospital stays, and 73% had fewer days of supplemental oxygen use.

Aerosolized Tobramycin (TOBI; Bethkis; Kitabis Pak)

KEY POINT

Nebulized tobramycin is used to manage chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF) as an alternative to intravenous therapy.

CLINICAL CONNECTION

Tobramycin is available as liquid nebulized solution and a dry powder inhaler, known as TOBI Podhaler.

Clinical Use

One disease state in which aerosolized antibiotics have been used more consistently for pulmonary infections is CF. Patients with CF are chronically infected with gram-negative organisms, such as *P. aeruginosa*, and the gram-positive bacterium *Staphylococcus aureus*, as well as other microorganisms. Chronic *Pseudomonas* infection leads to recurring acute respiratory infections. Apart from quinolone derivatives, such as ciprofloxacin, antibiotics that are effective against *Pseudomonas* do not give sufficient lung levels to inhibit bacteria when taken orally. Antibiotics with poor oral bioavailability for lung tissue include aminoglycosides, penicillin derivatives, and cephalosporins. Consequently, either the intravenous or the inhaled aerosol route must be used.

Baran et al.⁴⁹ administered 40 mg of gentamicin by aerosol to eight children with CF and found high levels of drug (>20 mcg/mL) in the bronchial secretions of seven of the children. Blood levels with the inhaled drug were low, supporting the case for minimal systemic toxicity by aerosol. Similar results with nebulized tobramycin (300 mg) were reported by Le Conte et al.⁵⁰ In contrast, intramuscular injection of 1.5 mg/kg gave low levels of less than 2 mcg/mL in bronchial secretions and, in some cases, undetectable levels.⁴⁹

Aerosol administration is attractive because of reduced cost potential and ease of use at home compared with intravenous therapy. Furthermore, fluoroquinolones, such as ciprofloxacin

and norfloxacin, which are active when taken orally, are not as suitable for prolonged maintenance or preventive therapy as the agents given by inhalation because of the risk of drug-resistant strains of bacteria. A report of the clinical trial establishing the safety and efficacy of inhaled tobramycin in managing *P. aeruginosa* in patients with CF was published by Ramsey et al.⁵¹ Inhaled tobramycin is used to manage chronic infection with *P. aeruginosa* in CF for the following reasons:

- To treat or prevent early colonization with *P. aeruginosa*
- To maintain present lung function or reduce the rate of deterioration

Efficacy with *Burkholderia cepacia* has not been shown using the inhaled route of administration.

Dosage and Administration

CLINICAL CONNECTION

Aerosolized tobramycin should be nebulized as a single agent in an approved nebulizer.

Inhaled tobramycin is recommended for children 6 years of age or older. The usual dosage is 300 mg twice daily approximately 12 hours apart and not less than 6 hours apart for 28 days consecutively, with the next 28 days off the drug. This cycle is repeated on a maintenance basis. Inhaled tobramycin has been studied with specific nebulizers. Any nebulizer other than one recommended by the manufacturer should be tested to ensure adequate drug output and particle size.

Patients should be instructed not to mix dornase alfa or any other drug with tobramycin in the nebulizer because of incompatibility with other drugs. Tobramycin should be inhaled after other therapies usually administered in CF, such as chest physiotherapy measures and other inhaled medications, including bronchodilators or dornase alfa, to allow for the greatest deposition of drug at the alveolar level.

Tobramycin is also available in dry powder form. TOBI Podhaler is a single-dose reusable dry powder inhaler (DPI), utilizing 28 mg capsules. Patients are prescribed four 28-mg capsules twice daily for 28 days. Because of the burden of treatment that patients with CF experience, the ease of use and short treatment time with TOBI Podhaler has found favorable results in patients regularly prescribed tobramycin, thus increasing adherence.^{52,53} Additionally, tobramycin is available as a co-package, Kitabis Pak. Kitabis Pak is 300 mg of tobramycin with a PARI nebulizer packaged as one.

Mechanism of Action

Tobramycin is a member of the aminoglycoside family of antibiotics. These antibiotics are effective in treating gram-negative infections and have a bactericidal effect, blocking protein synthesis in the bacteria and causing cellular death. Serum tobramycin levels are approximately 1 mcg/mL 1 hour after inhalation in patients with normal renal function.

Side Effects

Side effects for parenteral and inhaled administration of tobramycin are listed in Box 13.1. Adverse effects with *nebulized* delivery are based on the findings from the clinical trial by Ramsey et al.⁵¹ and on 2 years of clinical application after the FDA approval of inhaled tobramycin.

Side Effects With Parenteral Administration. Adverse effects that can occur with *parenteral* administration of aminoglycosides

• BOX 13.1 Side Effects of Aminoglycosides and Tobramycin

Parenteral Administration

- Ototoxicity (auditory and vestibular)
- Nephrotoxicity
- Neuromuscular blockade
- Hypomagnesemia
- Cross-allergenicity
- Fetal harm (deafness)

Inhaled Nebulized Tobramycin

- Voice alteration
- Tinnitus
- Nonsignificant increase in bacterial resistance

are reviewed briefly because the presence of impaired renal function or other conditions may increase the risk of these effects with inhaled administration.

Ototoxicity. Ototoxicity is associated with parenteral use of aminoglycosides. Ototoxicity manifests as auditory (cochlear) damage, with small loss of hearing at the higher frequencies or vestibular dysfunction with vertigo, nausea, or nystagmus (involuntary movement of eyeball).

Nephrotoxicity. Nephrotoxicity is also possible with aminoglycosides, which are excreted as unchanged drug through glomerular filtration. Although toxicity risk increases with dose, it may occur even with conventional doses in patients with prerenal azotemia or impaired renal function. Because excretion is by the renal system, impaired renal function can also increase risk of the other side effects noted.

Neuromuscular Blockade. Neuromuscular blockade is another side effect resulting from the potential curare-like effect of aminoglycosides on the neuromuscular junction. Neuromuscular blockade can aggravate muscle weakness, cause further worsening of neuromuscular disorders, or prolong and intensify neuromuscular blockade by curare-like paralyzing agents (see Chapter 18). *Hypomagnesemia* can occur in patients who have a poor or restricted diet.

Cross-Allergenicity. Cross-allergenicity exists among the aminoglycosides, and hypersensitivity to one agent in this group constitutes a contraindication to the use of other agents. The side effects cited are more likely with overdosage, poor renal function, and dehydration (resulting from higher renal concentrations with possible nephrotoxicity).

Fetal Harm. Fetal harm can occur with aminoglycosides because these drugs can cross the placenta. Irreversible bilateral congenital deafness has been reported in children of mothers who received streptomycin, another aminoglycoside.³⁷

Side Effects With Aerosolized Tobramycin. The only adverse effects reported after the 6-month clinical trial of Ramsey et al.⁵¹ were *tinnitus* and *voice alteration*. There was no hearing loss associated with nebulized use of tobramycin or changes in serum creatinine indicative of renal toxicity. There was a modest decrease in susceptibility of *P. aeruginosa* to tobramycin in the treatment group but not in the placebo group in the study by Ramsey et al.⁵¹ However, this was not associated with lack of clinical response to inhaled therapy with tobramycin. Use of an alternating schedule of administration may reduce the risk of drug resistance. Ramsey et al.⁵¹ noted that their rationale for intermittent administration of tobramycin was the observation that “drug holidays” allow

susceptible pathogens to repopulate the airway in patients with CF. Because tobramycin is delivered by inhalation, the airway concentration can be 100 times higher than the systemic levels. Thresholds of pathogen susceptibility with parenteral administration do not apply well to direct inhalation doses.

Precautions in Use of Aerosolized Tobramycin

- Inhaled tobramycin should be administered with caution to patients with preexisting renal, auditory, vestibular, or neuromuscular dysfunction.
- Admixture incompatibility exists between β -lactam antibiotics (penicillins and cephalosporins) and aminoglycosides when mixed directly together; tobramycin solution should not be mixed with antibiotics in this group, and mixing with other drugs generally is discouraged.
- Factors that could increase the risk of hearing damage with prolonged tobramycin use are renal impairment; concomitant dosage of parenteral aminoglycosides; dehydration; and concomitant use of ethacrynic acid, furosemide, or other ototoxic drugs.
- Nebulization of antibiotics during hospitalization should be performed under conditions of containment, as previously described for pentamidine and ribavirin, to prevent environmental saturation and development of resistant organisms in hospitals.
- Aminoglycosides can cause fetal harm if administered to pregnant women; exposure to ambient aerosol drug should be avoided by women who are pregnant or trying to become pregnant.
- *Local airway irritation* resulting in cough and bronchospasm with decreased ventilatory flow rates is a possibility with inhaled antibiotics and seems to be related to the osmolality of the solution.^{54–57} Peak flow rates and chest auscultation should be used before and after treatments to evaluate airway changes. Pretreatment with a β agonist may be needed.
- *Allergies* in the patient, staff, or family should be considered, if exposure to the aerosolized drug is not controlled. The use of a nebulizing system with scavenging filter, one-way valves, and thumb control could reduce ambient contamination with the drug, as previously described.

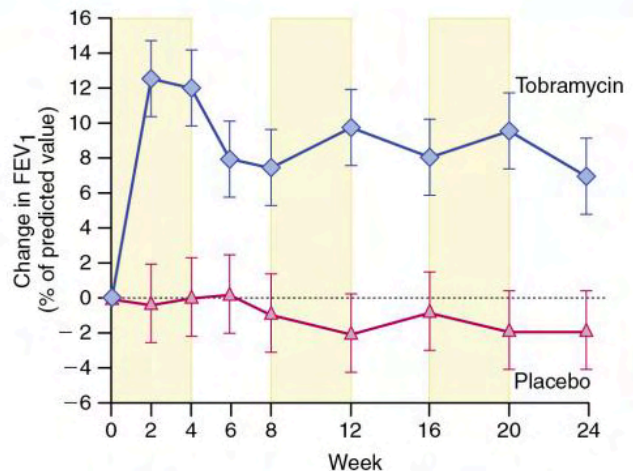
Clinical Efficacy

Clinical efficacy of inhaled tobramycin by nebulization was shown in the randomized controlled study by Ramsey et al.⁵¹ In that study, which compared inhaled tobramycin with placebo in 521 patients with CF, 6 months of alternating inhaled tobramycin and standard therapy for CF resulted in the following:

- Improved pulmonary function (Fig. 13.9)
- Decreased density of *P. aeruginosa* in expectorated sputum
- Reduced need for intravenous antipseudomonal antibiotics and hospitalizations
- No development of significant bacterial resistance

Other studies, such as that by Gibson et al.,⁵⁸ have reported similar results indicating that inhaled tobramycin is safe and effective in treating *P. aeruginosa* in patients with CF.

Because inhaled tobramycin is effective in patients with CF, is it effective in other patients with *P. aeruginosa* infection? LoBue⁵⁹ reported that either the studies, to date, have been small or the drug has not been used over the long term. Inhaled tobramycin cannot be recommended for treatment other than for patients with CF with *P. aeruginosa* infection.



• **Fig. 13.9** Mean change in forced expiratory volume in 1 second (FEV₁) from baseline for patients receiving inhaled tobramycin versus placebo. Bars represent 95% confidence intervals. (Modified from Ramsey, B. W., Pepe, M. S., Quan, J. M., et al. [1999]. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *New England Journal of Medicine*, 340, 23.)

Aerosolized Aztreonam (Cayston)

CLINICAL CONNECTION

Aerosolized aztreonam is used to improve *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF). Patients should be pretreated with a bronchodilator before administration of aerosolized aztreonam.

Clinical Use

Aztreonam was approved in December 1986 by the FDA as a monobactam, a synthetic bactericidal antibiotic; it is given as an intravenous solution. Inhaled aztreonam (Cayston) was approved in February 2010 to improve pulmonary symptoms in patients with CF colonized by *P. aeruginosa*. Cayston is not indicated for patients younger than 7 years of age or for those with *B. cepacia*. It has been studied only in patients with a forced expiratory volume in 1 second (FEV₁) greater than 25% or less than 75% of predicted.

Dosage and Administration

Cayston is supplied in a form that must be reconstituted. In a 28-day kit, each 2-mL single-use glass vial contains 75 mg of lyophilized aztreonam and must be mixed with the provided 1 mL of sterile diluent (0.17% sodium chloride). The reconstituted agent itself is delivered by using the Altera Nebulizer System (PARI Respiratory Equipment, Midlothian, Virginia).

Each patient should be pretreated with a bronchodilator before each dosing. Cayston is given three times a day for 28 days on and 28 days off. The kit should be refrigerated; however, when the kit is ready to use, it can be stored at room temperature for 28 days.

Any prescribed mucolytic should also be given before Cayston. In addition, any bronchial hygiene should be performed before administration of Cayston. Cayston has potential use as part of an alternating cycle of therapy with other inhaled therapies, such as inhaled tobramycin.

Mechanism of Action

Aztreonam displays *in vitro* activity against gram-negative aerobic bacteria. It binds to penicillin-binding proteins of pathogens,

such as *P. aeruginosa*, inhibiting bacterial cell wall synthesis and ultimately causing death of the cell.

Precautions in Use of Nebulized Aztreonam

As mentioned earlier, Cayston can cause bronchospasm and decrease a patient's FEV₁. All patients should be screened for baseline pulmonary function results and be treated with a bronchodilator before administration of Cayston.

It has been reported that patients have experienced severe allergic reactions with injectable aztreonam. Careful observation is warranted when first using Cayston because it could cause an allergic reaction. If any signs occur during the delivery of Cayston, the treatment should be stopped immediately and the health care team should be informed.

The use of antibiotics in the absence of infection may lead to the development of drug-resistant bacteria. Cayston should not be used in patients with CF not infected by *P. aeruginosa*.

General Considerations in Aerosolizing Antibiotics

Several points should be noted when nebulizing antibiotic drugs, especially if an injectable formulation is used, although this is *not* recommended for routine clinical use.

- Antibiotic solutions, such as gentamicin, are more viscous than bronchodilator solutions, and this may affect nebulizer performance. Compressors must be suitably powerful; high-flow compressors are suggested.⁶⁰ Flow rates of 10 to 12 L/min have also been suggested by Newman et al.⁶¹ for suitably small particle sizes with antibiotic solutions.
- Environmental contamination in health care agencies and practitioner exposure to the aerosolized drug can be reduced by using expiratory filters with one-way valves and a thumb control, as with aerosolized pentamidine.
- Hata and Fick⁶² noted physical incompatibility between some antibiotics. Aminoglycosides, such as gentamicin, are chemically inactivated by carbenicillin and piperacillin when mixed together. These drugs should be given in separate nebulizer treatments, and this has the disadvantage of requiring twice the treatment time. Any antibiotic combination and other drug combinations should at least be inspected for visible changes, such as discoloration or precipitation and should not be used if such changes are observed.

Ideally, drug mixtures for nebulization should be tested for chemical compatibility in addition to a visual inspection.

Inhaled Zanamivir (Relenza)

CLINICAL CONNECTION

Zanamivir is available for administration with a dry powder inhaler (DPI) to treat acute symptoms of influenza. This agent may cause bronchospasm and should not be used in patients with preexisting lung disease.

Clinical Use

Zanamivir (Relenza) is an antiviral agent approved for use in the treatment of uncomplicated influenza illness in adults and children older than 7 years of age during the early onset (within the first 2 days) of infection. The medication may be used prophylactically in children as young as 5 years of age. The agent has an off-label use for treatment and prophylaxis of H1N1 influenza A ("swine flu"). An oral anti-influenza agent, oseltamivir phosphate (Tamiflu), is also available as 30-mg, 45-mg, and 75-mg capsules and 12 mg/mL oral liquid. It is indicated in the treatment and prophylaxis of influenza in patients 1 year of age and older. Tamiflu has an off-label use in H1N1 influenza A. In addition, two older-generation drugs, amantadine and rimantadine, have been used for prophylaxis and treatment of acute symptoms of influenza. Table 13.2 summarizes the information on these four agents, only one of which (zanamivir) is available as an inhalant. Prophylactic vaccination against influenza, especially in patients at high risk for cardiovascular or respiratory disease, remains the unqualified recommendation despite the availability of drugs to treat acute infection.

Dosage and Administration

Zanamivir is available as a DPI, the Diskhaler device, for oral inhalation. Each blister contains 5 mg of drug, providing a dose of 5 mg per inhalation. There are four blisters in a Rotadisk, and the drug package contains five Rotadisks with one Diskhaler device. The dose for adults and children 5 years of age or older is two inhalations (two blisters, for a total of 10 mg) taken twice a day approximately 12 hours apart for 5 days. The complete drug package has the equivalent of 5 days of treatment because each

TABLE 13.2 Antiviral Agents Used to Treat or Prevent Influenza

Drug	Brand Name	FDA Approval	Activity	Clinical Use	Route of Administration	Adult Dosage
Peramivir	Rapivab	2014	Influenza A and B	Prophylaxis, acute treatment	IV	600 mg/day
Rimantadine	Flumadine	1993	Influenza A	Prophylaxis, acute treatment	Oral: tablet	100 mg bid
Oseltamivir	Tamiflu	1999	Influenza A and B; H1N1 ("swine flu")	Prophylaxis, acute treatment	Oral: capsule, liquid suspension	12 mg,* 75 mg bid, for 5 days
Zanamivir	Relenza	1999	Influenza A and B; H1N1 ("swine flu")	Prophylaxis, acute treatment	DPI: Diskhaler	10 mg (2 inhalations) bid, for 5 days
Baloxavir Marboxil	Xofluza	2018	Influenza A and B	Prophylaxis, acute treatment	Oral tablet, liquid suspension	40–80 mg based on weight

*Depends on weight of child; see manufacturer's dosing schedule.

bid, Twice daily; DPI, dry powder inhaler; FDA, US Food and Drug Administration.

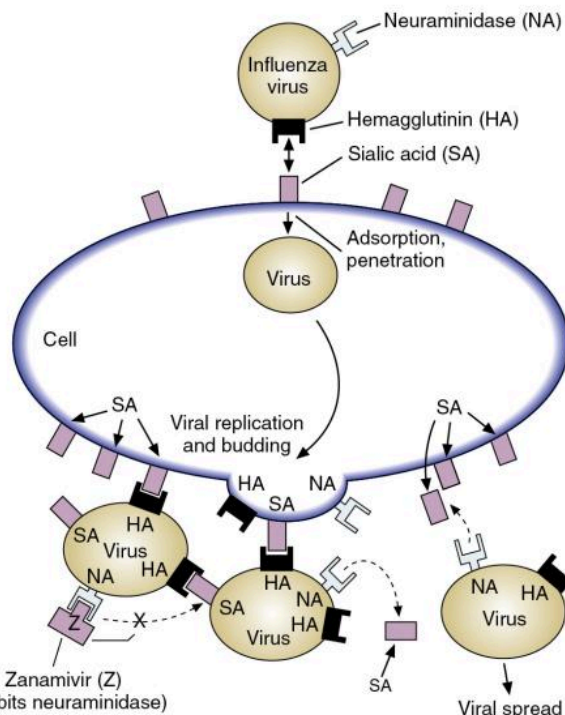
Rotadisk contains 1 day's dosage. Patients should finish the entire 5-day course of drug.

Mechanism of Action

The general mechanism of viral infection was described previously with ribavirin (see the discussion on the nature of viral infection). Zanamivir represents a new class of antiviral agents, termed *neuraminidase inhibitors*, which act by binding to the viral enzyme neuraminidase (NA) and blocking the action of the enzyme. The influenza virus has an envelope and a protein coat surrounding the viral RNA and targets the respiratory tract. Briefly, as illustrated in Fig. 13.10, the virus envelopes for both *influenza A* and *influenza B* have two surface glycoproteins, *hemagglutinin (HA)* and *NA*.

HA binds to a sugary molecule, *sialic acid (SA)*, on the surface of a cell to be infected. This binding leads to fusion of virus and cell membranes and allows adsorption and penetration of the virus into the cell. However, when the newly minted viral particles bud from the cell and are ready to be released, the viral envelope acquires SA from the cell, along with its own HA and NA receptors. Without NA, the viral HA would combine with the SA again, "sticking" the viral particles to each other and to the cell surface, preventing further infection. NA cleaves part of the SA to prevent HA and SA combination and prevents viral aggregation (clumping). NA is essential for virus release from infected cells, prevents virus aggregation, and may decrease virus inactivation by respiratory mucus. Zanamivir is able to bind to NA and block the enzyme action. By inhibiting NA, zanamivir inhibits viral particle separation and cellular release needed for systemic infection to proceed.⁶³

Zanamivir is given by inhalation because the binding ability of the drug also prevents good absorption when given orally.



• **Fig. 13.10** Simplified illustration of mechanism of action by which inhaled zanamivir (Z) provides its antiviral effect in influenza viral infection. As a sialic acid (SA) analog, zanamivir binds to the enzyme neuraminidase (NA) and inhibits its usual inactivation of SA. As a result, the viral hemagglutinin (HA) receptor continues to combine with both cell and viral SA, causing viral aggregation and preventing viral release and spread.

Inhalation also delivers the drug to the affected organ directly. Approximately 4% to 17% of an inhaled dose is absorbed systemically. Zanamivir has limited plasma protein binding (<10%) and is excreted unchanged in the renal system. It is apparently not metabolized to other products in vivo. Its serum half-life is 2.5 to 5.1 hours. Any unabsorbed drug is excreted in feces.

Adverse Effects

The side effects discussed in the following sections have been noted during clinical trials and after release of zanamivir.

Bronchospasm and Deterioration of Lung Function. Patients with underlying respiratory disease, such as asthma or COPD, may experience bronchospasm after inhaling zanamivir. Respiratory difficulty and wheezing have been reported in a patient with COPD⁶⁴ and a patient with asthma inhaling zanamivir.⁶⁵ Apparently neither of these patients had influenza at the time of treatment. In a clinical trial of zanamivir by Cass et al.,⁶⁶ which included 11 patients with mild to moderate asthma and no influenza, no symptoms of bronchospasm or airway responsiveness were observed. However, such data do not establish the safety of zanamivir in patients with asthma with influenza infection, which can cause mucosal damage and airway reactivity from the viral inflammation.^{67,68} In ongoing treatment studies of patients with COPD or asthma who had influenza-like illness, more patients receiving zanamivir compared with patients receiving a placebo had a greater than 20% decline in FEV₁ or peak expiratory flow rate.⁶³ Zanamivir should be discontinued if bronchospasm or a decline in lung function occurs in any patient, and the managing physician should be consulted. The manufacturer advises against zanamivir use in any patient with underlying airways disease.³⁷

Undertreatment of Bacterial Infection. Bacterial respiratory infections can manifest with influenza-like symptoms, and viral respiratory infections can progress to serious bacterial secondary infections.⁶⁸ Treatment with an antiviral agent, such as zanamivir, is ineffective against bacterial infection and could possibly allow progression of the infection to a serious illness, such as pneumonia. Two deaths from bacterial infection in subjects taking zanamivir have been reported,⁶⁹ although the reasons were not determined.⁷⁰ Inadequate treatment of COPD exacerbation may result in serious complications and thus hospitalization.⁶⁸

Allergic Reactions. As with any drug, patients should be monitored for allergic or allergic-like reactions with zanamivir.

Other Adverse Effects. Adverse reactions occurring in a small percentage of patients included gastrointestinal (diarrhea, nausea, vomiting) and respiratory effects (bronchitis; cough; sinusitis; ear, nose, and throat infections), dizziness, and headaches. These reactions did not differ substantially from reactions with placebos and may have been caused by the same lactose vehicle used in the active drug or in the placebo.

Clinical Efficacy and Safety

Clinical efficacy of zanamivir has been established in trials showing that inhaled zanamivir can significantly shorten the duration of influenza symptoms.^{67,70,71} With uncomplicated influenza-like illness, treatment with 10 mg of zanamivir twice daily resulted in approximately 1 day of shortening of the median time to improvement in symptoms compared with a placebo.⁶⁷ The time to improvement in major symptoms was defined as no fever and no or mild headache, myalgia, cough, and sore throat. Among patients who were febrile and began treatment 30 hours or less after onset of symptoms, treatment with zanamivir resulted in a shortening of 3 days in the median time to alleviation of symptoms.⁶⁷ There are no data on efficacy when zanamivir is started after more than 2 days of symptoms of influenza.

There was no consistent difference in treatment effect between patients with influenza A versus influenza B. However, the clinical trials of zanamivir enrolled predominantly patients with influenza A (89% influenza A versus 11% influenza B in one clinical trial). Patients with lower temperature and less severe symptoms in general derived less benefit from treatment with zanamivir.

Clinical trials of zanamivir were performed mainly with previously healthy subjects.^{67,70,71} The manufacturer's literature states that safety and efficacy of zanamivir for treating influenza have not been shown in patients with COPD. Zanamivir may carry risk for patients with COPD or asthma, as indicated in the discussion of side effects. Revised labeling for zanamivir adds a warning that zanamivir is *not generally recommended for patients with underlying airways disease* because of the risk of serious adverse effects.⁶⁷

Zanamivir is not approved for prophylaxis to prevent influenza, and it does not reduce the risk of transmission of the virus to others. However, some data suggest a prophylactic benefit with zanamivir in influenza A and influenza B in university and nursing home communities.⁷² Results of a controlled study of inhaled zanamivir for treatment and prevention of influenza in families in which one member developed influenza-like illness showed that zanamivir did reduce the rate of developing influenza in other family members. The proportion of families in which an initially healthy member developed influenza was 4% with zanamivir compared with 19% with a placebo.⁷³ In the trial, treatment of the index cases with zanamivir in families reduced the median duration of symptoms from 7.5 to 5 days, a significant reduction. Oseltamivir (Tamiflu) was approved for prevention of influenza A and influenza B in children 1 year of age or older in close contact with influenza cases. Adverse reactions were similar in both groups.³⁷

The safety and efficacy of zanamivir have been tested in children. In a study by Hedrick et al.,⁷⁴ zanamivir was tested on children 5 to 12 years of age. In the study of 471 children, 224 were given zanamivir, and the remaining children, the control group, were given a placebo. The children taking zanamivir had reduced influenza symptoms 1.25 days before children in the placebo group. The zanamivir group returned to normal activities in less time and took fewer relief medications compared with the placebo group.

A final issue with the use of zanamivir or other antiinfluenza agents as acute treatment is the lack of a clinically easy and inexpensive diagnostic tool to confirm the presence of influenza infection. Zanamivir is not beneficial in patients with infections other than influenza. In the clinical trial by Hayden et al.,⁶⁷ 262 of 417 patients (63%) with influenza-like illness had confirmed influenza virus infection. As a result, symptoms alone can result in inappropriate use of antiinfluenza drugs, with attendant risks as outlined in the discussion of adverse effects. Inappropriate use contributes to increased cost.

The cost versus efficacy of zanamivir has been debated. There is modest reduction in symptoms for the cost of the drug; there is no readily available test to confirm the presence of influenza viral infection for use of the drug, resulting in possibly inappropriate use; and the drug carries increased risk for the patients who might benefit most—patients with reactive airways disease.

RESPIRATORY CARE ASSESSMENT OF AEROSOLIZED ANTIINFECTIVE AGENTS

Before Treatment

The following assessment applies to all the aerosolized antiinfective agents discussed:

- Assess for presence of disease indicating appropriate use of agent:
 - *Pentamidine*: Risk of PJP
 - *Ribavirin*: Presence of severe RSV infection in infants or children at risk
 - *Tobramycin*: Chronic *P. aeruginosa* infection compromising lung function in patients with CF
 - *Aztreonam*: Chronic *P. aeruginosa* infection compromising lung function in patients with CF
 - *Zanamivir*: Symptoms of acute influenza infection within first 2 days of onset
- Assess correct configuration and function of aerosol equipment for ribavirin; instruct and verify correct use of aerosol delivery device for other agents.
- On initial aerosol treatment, assess respiratory rate and pattern, pulse, and breath sounds; evaluate for presence of airway irritation resulting in wheezing and bronchospasm.

During Treatment and Short Term

Pentamidine

- Monitor for coughing and bronchospasm, and if these are present, provide a short-acting β agonist or an anticholinergic bronchodilator, such as ipratropium with inhaled pentamidine.
- Monitor for occurrence rate of PCP and rate of hospitalizations over the long term.
- Monitor for presence of side effects (shortness of breath, possible pneumothorax, conjunctivitis, rash, neutropenia, dysglycemia) or appearance of extrapulmonary *P. jiroveci* infection.

Ribavirin

- Monitor for signs of RSV infection severity for improvement, including vital signs, respiratory pattern and work of breathing (clinically), level of fraction of inspired oxygen (FiO_2) needed, level of ventilatory support, arterial blood gases, body temperature, and other indicators of pulmonary gas exchange.
- Monitor patient for evidence of side effects, such as deterioration in lung function, bronchospasm, occlusion of endotracheal tube, if present, cardiovascular instability, skin irritation from the aerosol drug, and equipment malfunction caused by drug residue.

Tobramycin

- Verify that patient understands that nebulized tobramycin should be given after other inhaled medications for CF.
- Check whether patient has renal, auditory, vestibular, or neuromuscular problems or is taking other aminoglycosides or ototoxic drugs. Consider whether tobramycin should be given, based on severity of preexisting or concomitant risk factors.
- Monitor lung function to note improvement in FEV_1 .
- Assess rate of hospitalization before and after institution of inhaled tobramycin.
- Assess need for intravenous antipseudomonal therapy.
- Assess improvement in weight.
- Monitor for occurrence of side effects such as tinnitus or voice alteration; have patient rinse mouth after aerosol treatments.
- Evaluate for changes in hearing function or renal function during use of inhaled tobramycin.

Aztreonam

- Verify that patient understands that nebulized aztreonam should be given after other inhaled medications for CF.

- Monitor lung function to note improvement in FEV_1 .
- Assess rate of hospitalization before and after institution of inhaled aztreonam.
- Monitor for occurrence of side effects, such as an allergic reaction; have patient rinse mouth after aerosol treatments.

Zanamivir

- Assess improvement in influenza symptoms: fever reduction, less myalgia and headache, reduced coughing and sore throat, and less systemic fatigue.
- Monitor for airway irritation and symptoms of bronchospasm, especially during initial use of the dry powder aerosol. Provide a short-acting β agonist, if needed, or if patient is at risk for airway reactivity (COPD, asthma).

Long Term

- Monitor pulmonary function studies of lung volumes, capacities, and flows.
- Instruct patients with CF in use and interpretation of disposable peak flow meters to assess severity of CF episodes and to ensure there is an action plan for treatment modification.
- Instruct and verify correct use of the aerosol delivery device (SVN, MDI, reservoir, DPI).
- Instruct patients in the use, assembly, and especially cleaning of aerosol inhalation devices.

General Contraindications

Pentamidine

- Bronchospasm and cough are common; pretreat with a bronchodilator.
- Use with a nebulizer system with a one-way valve and expiratory filter system to decrease caregiver exposure.

Ribavirin

- Caregivers who are pregnant or wish to become pregnant should avoid exposure; the effect on fertility is uncertain.

Tobramycin

- Drug resistance is the greatest risk with use of this agent; using an alternating schedule should help.

Aztreonam

- Drug resistance is the greatest risk with use of this agent; using an alternating schedule should help.
- Aztreonam should not be used in patients with CF not infected with *P. aeruginosa*.

Zanamivir

- Patients with preexisting and uncontrolled airways disease should not use this agent; bronchospasm and lung deterioration may occur.

2. Briefly explain the rationale for aerosolizing an antibiotic, such as tobramycin or aztreonam, in CF.
3. What is the brand name of aerosolized pentamidine?
4. What is the dose and frequency for aerosolized pentamidine?
5. What device is approved for aerosolization of pentamidine?
6. Identify the common airway effects with aerosolized pentamidine and suggest a method for preventing or lessening these effects.
7. What is a major risk to the caregiver when aerosolizing pentamidine to a patient with AIDS?
8. What is the current CDC-recommended prophylactic treatment for PCP in patients with AIDS?
9. What is the brand name and dose for aerosol ribavirin?
10. What is the mechanism of action of ribavirin?
11. Name two serious hazards when ribavirin is given to a patient undergoing mechanical ventilation.
12. In general, how can you prevent environmental contamination when delivering ribavirin to an oxygen hood?
13. What is the recommended dosage for inhaled tobramycin?
14. Identify common side effects that have been observed with aerosolized tobramycin.
15. Name two potential hazards to family members with aerosolized tobramycin at home.
16. What is the recommended dosage for inhaled aztreonam?
17. What should be done before a patient is prescribed inhaled aztreonam?
18. Give the brand name and dosage for zanamivir.
19. In one sentence, describe the mechanism of action of zanamivir.
20. Identify common hazards in the use of inhaled zanamivir.
21. What factors cause debate over the use of zanamivir in treating influenza?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

Brody Hendrix is a 29-year-old man with cystic fibrosis (CF). The history of his disease and its previous treatment are well known to his pulmonary physician. He has been admitted to the hospital with complaints of increasing cough, shortness of breath, and sputum production. He reports that his sputum is greenish. His recent history reveals that his last admission for exacerbation of CF was approximately 6 months ago. He has used albuterol by metered dose inhaler (MDI), with two puffs four times daily (qid), and recently began to use salmeterol, two puffs twice daily (bid). He maintains himself on a regular regimen of CF medications, including iron and vitamin supplements and pancrelipase (Pancrease). Approximately 3 weeks ago, he complained of increasing pulmonary secretions and noted a mild elevation of his temperature (99.1°F). At that time, his physician prescribed ciprofloxacin, 500 mg orally bid, and he completed a course of 14 days, ending 5 days ago.

He is alert, oriented, and in no acute distress at this time. His skin is warm and dry. Vital signs are as follows: blood pressure (BP) of 106/66 mm Hg, pulse (P) of 88 beats per minute (beats/min), regular respiratory rate (RR) of 20 breaths per minute (breaths/min), and temperature (T) of 98.9°F. His respiratory pattern is normal, and there is no use of accessory muscles. Auscultation reveals scattered rales and wheezes bilaterally, both anteriorly and posteriorly. His cough is nonproductive during the examination.

A chest radiograph shows hyperexpanded lung fields, with linear fibrotic changes bilaterally over the lung fields. Cardiac silhouette shows mild right atrial hypertrophy. No consolidation or pleural effusion is seen. Complete blood count (CBC) results are as follows: hemoglobin of 13.2 g/dL, hematocrit at 38.6%, and white blood cell (WBC) count of $13.5 \times 10^3/\text{mm}^3$. Other blood values are normal. Pulse oximetry measures 89% saturation on room air. Pulmonary function testing, performed approximately 2 months ago and available in his chart, shows the following:

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify the disease states for which each of these drugs is used when inhaled as an aerosol: pentamidine, ribavirin, tobramycin, aztreonam, and zanamivir.

	Observed	Predicted	Percent Predicted
Total lung capacity (TLC), L	7.66	6.67	115
Forced vital capacity (FVC), L	3.52	5.23	67
Forced expiratory volume in 1 second (FEV ₁), L	1.41	3.51	40
Mean forced expiratory flow during middle half of FVC (FEF ₂₅₋₇₅), L/sec	0.49	2.93	17
Expiratory reserve volume (ERV), L	0.94	1.69	56
Residual volume (RV), L	4.0	1.54	260

A sputum culture sample is taken and sent to the laboratory. Mr. Hendrix is admitted for acute exacerbation of his pulmonary symptoms.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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14

Antimicrobial Agents

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CHAPTER OUTLINE

Principles of Antimicrobial Therapy

Identification of Pathogen

Susceptibility Testing and Resistance

Host Factors

Pharmacodynamics

Antimicrobial Combinations

Monitoring Response to Therapy

Antibiotics

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Clinical Uses

Adverse Reactions and Precautions

Cephalosporins

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Carbapenems

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Monobactams (Aztreonam)

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Aminoglycosides

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Tetracyclines

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Tetracycline Derivatives

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Macrolides, Azalides, and Ketolides

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Fluoroquinolones

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

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Trimethoprim-Sulfamethoxazole

Clindamycin

Metronidazole

Glycopeptides

Quinupristin and Dalfopristin

Oxazolidinones

Antimycobacterials

Isoniazid

Mechanism of Action

Adverse Reactions and Precautions

Rifampin, Rifabutin, and Rifapentine

Mechanism of Action

Adverse Reactions and Precautions

Pyrazinamide

Mechanism of Action

Adverse Reactions and Precautions

Ethambutol

Mechanism of Action

Adverse Reactions and Precautions

Streptomycin

Mechanism of Action

Adverse Reactions and Precautions

Antifungals

Polyenes

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Azoles

Mechanism of Action

Clinical Uses

Adverse Reactions and Precautions

Echinocandins*Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Flucytosine***Mechanism of Action**Clinical Use**Adverse Reactions and Precautions***Antiviral Agents****Acyclovir and Valacyclovir***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Penciclovir and Famciclovir***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Ganciclovir and Valganciclovir***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Cidofovir***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Foscarnet***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Amantadine and Rimantadine***Mechanism of Action**Clinical Uses**Adverse Reactions***Oseltamivir, Zanamavir, and Peramivir***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Baloxavir Marboxil***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions**Mechanism of Action**Molnupiravir and Nirmatrelvir/Ritonavir***Biologics****COVID-19 and Monoclonal Antibodies****Raxibacumab and Obiltoximab***Mechanism of Action**Clinical Uses**Adverse Reactions and Precautions***Respiratory Care Assessment of Antibiotic Therapy**

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

OBJECTIVES*After reading this chapter, the reader will be able to:*

1. Define terms that pertain to antimicrobial agents
2. Define *antibiotic*
3. Describe the process involved in bacterial susceptibility testing
4. Discuss possible outcomes of antimicrobial combinations
5. List the various classes of penicillins
6. List the various classes of cephalosporins
7. Recognize similarities between members of macrolides, azalides, and ketolides
8. Recognize similarities between members of fluoroquinolones
9. List four mechanisms of action of antibacterials
10. List five commonly used antimycobacterials
11. Describe the commonly used azole antifungals and how they differ in spectrum of activity
12. Discuss similarities between members of echinocandins
13. Describe mechanisms of action of antiretrovirals
14. Describe agents used to treat COVID-19

KEY TERMS AND DEFINITIONS

Antagonism Antibiotic combination in which the activity of one antibiotic interferes with the activity of the other (block receptor site, enzymatic inactivation), resulting in less activity with the combination than with the individual drugs.

Antibiotics Substance derived or produced from a microorganism that inhibits or kills other microorganisms.

Antimicrobials Natural and synthetic compounds that either inhibit or kill microorganisms.

Synergy The combined effect of two antimicrobials is greater than their added effect (i.e., increased permeability by one agent allows the second agent access to the bacterial target).

Antimicrobials are among the most widely used therapeutic agents in the world. A variety of antimicrobial agents have been developed from naturally occurring compounds or created synthetically. The development of new classes of antimicrobials (i.e., those with a novel mechanism of action) has declined in recent years, with most new agents coming from chemical modification of older agents. This presents a challenge to clinicians because

microbes are developing resistance to many commonly used antimicrobial agents.

Techniques to identify organisms¹ and to determine their susceptibility^{2,3} have evolved over the years and are vital for selection of effective antimicrobial therapy. In addition, other factors, such as host factors, antimicrobial pharmacodynamics, antimicrobial combinations, and methods of monitoring therapy, are important

parameters that need consideration before selecting an antimicrobial agent.⁴⁻⁶ This chapter focuses on these basic principles of antimicrobial therapy, provides a synopsis of mechanism of action and adverse effects, and emphasizes the clinical use of the various antimicrobial classes for the treatment of respiratory infections.

Principles of Antimicrobial Therapy

Several factors require careful consideration before choosing a particular antimicrobial agent.⁴⁻⁶ Identification of the organism or organisms responsible for the infection is the first step toward treatment. Before initiating antimicrobial therapy, diagnostic specimens should be properly collected and promptly submitted to the microbiology laboratory.^{1,4,6} Results from these tests may not be available for 24 to 72 hours, so initial therapy is guided by the clinical presentation of the patient.⁴⁻⁶ Empiric therapy is often based on evidence-based practice guidelines. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) have published guidelines for the management of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), with elimination of health care–associated pneumonia (HCAP) from the 2016 IDSA HAP/VAP guidelines.^{7,8} Once an organism is isolated, antimicrobial susceptibility is determined according to standardized methods that can be replicated among laboratories, such as those established by the Clinical and Laboratory Standards Institute (CLSI). The susceptibility pattern of the organism narrows the choice of potential agents. The choice of a specific agent is also influenced by host factors (drug allergies, organ function, infection site) and drug factors (available dosage forms, cost).

Identification of Pathogen

The first step toward identification of potential pathogens is the collection of specimens for culture. Specimens commonly collected include blood, urine, sputum, cerebrospinal fluid, pleural fluid, synovial fluid, peritoneal fluid, and stool.⁶ Several methods are employed to identify the pathogens rapidly using various chemical stains, immunologic assays, and microscopic examination.¹ The simplest and most common preparation is the Gram stain. This stain designates bacteria into two major classes: gram-positive bacteria (which stain purple) and gram-negative bacteria (which stain red). Bacteria stain differently, depending on the structural components of their cell walls. These structural components also affect their susceptibility to antimicrobials. The Gram stain also distinguishes bacteria from one another on the basis of their morphology. Spheric bacteria, such as *Staphylococcus* and *Streptococcus* species, are cocci, and rod-shaped bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, are bacilli. Other bacteria, such as *Mycobacterium tuberculosis*, require the use of an acid-fast stain to penetrate their wax-like cell walls. Mycobacteria generally require 10 to 14 days for growth but may take as long as 6 weeks, and this makes acid-fast staining vital for the rapid diagnosis of tuberculosis.⁶ Certain fungi can be quickly identified by using India ink (for *Cryptococcus neoformans*) and potassium hydroxide (KOH) preparations. Urinary antigen tests may be performed for rapid identification of *Streptococcus pneumoniae* and *Legionella pneumophila*. Rapid antigen tests for influenza allow detection, as well as to distinguish between influenza A and B.^{1,7,9}

In many clinical cases, the exact identity of the infecting organism is unknown. As a result, patients are treated empirically with an antimicrobial agent active against the organism or organisms

most likely causing the infection.⁶ For example, 40% or greater of patients with CAP fail to expectorate sputum, preventing identification of a specific pathogen.⁷ Collective data from numerous studies have the most common pathogens responsible for CAP include *S. pneumoniae*, *Haemophilus influenzae*, and atypical (intracellular) organisms, such as *Mycoplasma pneumoniae*, *Chlamydia* (formerly *Chlamydia*) *pneumoniae*, and *L. pneumophila*. As a result, empiric therapy for CAP involves antimicrobials active against this spectrum of organisms.^{7,9} Conversely, identification of an organism from culture material does not necessarily indicate an infection.⁶ For example, hospitalized patients often have growth of gram-negative bacilli in sputum samples. However, these organisms may only represent colonization and not HAP (also known as nosocomial pneumonia). In addition, specimens obtained after initiation of antimicrobial therapy may not be reliable, as *S. pneumoniae* and other pathogens may be masked by overgrowth of normal microbial flora.^{1,7,8}

Common pathogens and treatment of specific respiratory infections are listed in Table 14.1.

Susceptibility Testing and Resistance

KEY POINT

The susceptibility of an organism to an antimicrobial is quantified as the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC).²⁻⁴ The science of understanding the optimal effect of an antimicrobial as a function of its concentration to the MIC against the microorganism is known as *pharmacodynamics*.⁴⁻⁶

CLINICAL CONNECTION

It is not uncommon for a patient to receive antibiotic therapy before susceptibility and resistance testing results are obtained. The testing will assist in providing better antibiotic therapy coverage to the patient.

Once an organism is isolated, susceptibility test results can usually be obtained within 24 hours. Several methods are commonly used to determine the susceptibility of isolated pathogens.^{2,3} The Kirby-Bauer disk diffusion test involves the use of antibiotic-impregnated disks that are placed on an agar plate heavily inoculated (105 colony-forming units per milliliter [cfu/mL]) with the isolated bacteria. If the organism is susceptible to the antibiotic, a clear zone of inhibition (no growth of the organism) develops around the disk. Published breakpoints for the diameter of the clear zones are used to determine whether the organism is susceptible or resistant to the antimicrobial agent. However, they do not provide specific data on the concentration needed to kill or inhibit growth of the organism. Another disk diffusion test is the elliptical test, or E-test. The E-test strip is placed on an agar plate heavily inoculated with the isolated organism. The strip creates an antimicrobial gradient, which results in a clear elliptical zone of inhibition. This method allows for the determination of the minimal inhibitory concentration (MIC). MIC is defined as the least concentration of antimicrobial that prevents visible growth.²⁻⁴ The Kirby-Bauer and E-test methods are illustrated in Fig. 14.1.

Other methods include inoculation of the organism into serial dilutions of an antimicrobial in agar or, more commonly, in broth culture media (Fig. 14.2). Automated systems, such as Vitek (bioMérieux, Durham, North Carolina), MicroScan (Siemens Medical Solutions, Malvern, Pennsylvania), and BD Phoenix (Becton

TABLE 14.1 Common Pathogens and Treatment of Respiratory Infections in Adults^{70–79}

Respiratory Infection	Common Pathogens	Potential Antibiotic Regimens
Rhinosinusitis ^{70,71,*}		
Acute (community acquired)	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , viruses (rhinovirus, adenovirus, coronavirus)	Amoxicillin-clavulanate is drug of choice; doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) for penicillin-allergic patients
Acute (hospital acquired)	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , Enterobacteriaceae	Antipseudomonal β -lactam (ceftazidime, cefepime, or aztreonam) or an antipseudomonal carbapenem (imipenem or meropenem) and vancomycin
Chronic	Predominantly anaerobes (<i>Prevotella</i> spp., <i>Porphyromonas</i> spp., <i>Peptostreptococcus</i> spp., <i>Fusobacterium</i> spp.), <i>S. aureus</i> , <i>P. aeruginosa</i>	Antibiotics are usually not indicated; amoxicillin-clavulanate and azithromycin often used
Bronchitis ^{72,73,*}		
Acute	Predominantly respiratory viruses (influenza A and B, parainfluenza, RSV), <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , <i>Bordetella pertussis</i>	Antibiotics are usually not indicated; however, doxycycline or azithromycin may be considered
Exacerbation of chronic bronchitis	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i>	Value of antibiotics is controversial; doxycycline or azithromycin may be considered
Pneumonia ^{74–78,*}		
Outpatient	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , <i>H. influenzae</i> , <i>C. pneumoniae</i> , and respiratory viruses	Azithromycin, doxycycline, respiratory fluoroquinolone, or β -lactam (amoxicillin-clavulanate, cefuroxime) plus, azithromycin
Inpatient (non-ICU)	As indicated for outpatient, plus <i>Legionella pneumophila</i>	Respiratory fluoroquinolone or β -lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam) plus azithromycin
Inpatient (ICU)	<i>S. pneumoniae</i> , <i>S. aureus</i> , <i>L. pneumophila</i> , <i>H. influenzae</i> , Enterobacteriaceae	β -Lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam) plus azithromycin or respiratory fluoroquinolone
	If risk for <i>P. aeruginosa</i>	Antipneumococcal, antipseudomonal β -lactam (piperacillin-tazobactam, cefepime, ceftazidime, or antipseudomonal carbapenem) plus ciprofloxacin, levofloxacin, or aminoglycoside
	If risk for <i>S. aureus</i>	Add vancomycin or linezolid
Hospital acquired	<i>S. pneumoniae</i> , <i>S. aureus</i> , including MRSA, <i>P. aeruginosa</i> , Enterobacteriaceae	Cefepime, ceftazidime, piperacillin-tazobactam, aztreonam, or antipseudomonal carbapenem $\pm$ aminoglycoside, ciprofloxacin, or levofloxacin $\pm$ vancomycin or linezolid
Hospital acquired (neutropenic patient)	As listed for patients with neutropenia, and fungi, such as <i>Candida</i> spp., <i>Aspergillus</i> spp., and if HIV positive, <i>Pneumocystis jiroveci</i> (formerly <i>P. carinii</i> [PCP])	As listed for nonneutropenic $\pm$ amphotericin B (commonly lipid formulations), azoles (fluconazole or voriconazole), or echinocandins (caspofungin, micafungin, anidulafungin) $\pm$ TMP-SMX
Aspiration suspected	Anaerobes (<i>Bacteroides</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp.) and aerobes (<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> , Enterobacteriaceae)	β -Lactam/ β -lactamase inhibitor (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam), or clindamycin, carbapenem, or moxifloxacin.
Patient with cystic fibrosis	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Burkholderia cepacia</i> complex, <i>Achromobacter xylosoxidans</i> , <i>Stenotrophomonas maltophilia</i>	Aminoglycoside or ciprofloxacin plus piperacillin-tazobactam or ceftazidime, cefepime or antipseudomonal carbapenem $\pm$ TMP-SMX (<i>B. cepacia</i> complex, <i>S. maltophilia</i>) $\pm$ vancomycin
Empyema ⁷⁹	<i>Streptococcus milleri</i> group, <i>Bacteroides fragilis</i> group, <i>Prevotella</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp., <i>S. pneumoniae</i> , <i>S. aureus</i> , Enterobacteriaceae	β -Lactam/ β -lactamase inhibitor, carbapenem, or third-generation cephalosporin (ceftriaxone) plus clindamycin or metronidazole $\pm$ vancomycin

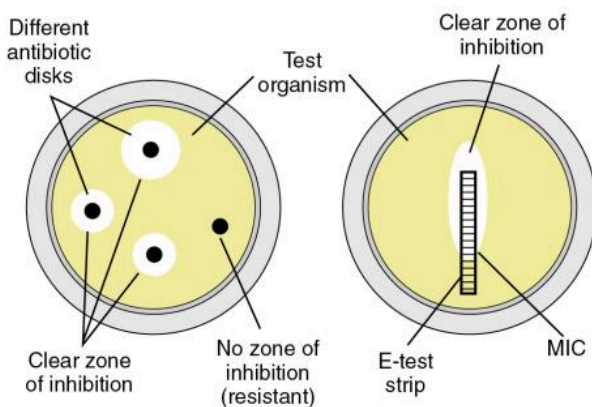
*The potential treatments listed here are not listed in order of superiority. Choice of antimicrobials depends on the individual susceptibility pattern of the suspected organisms within the specific institution or community and host factors.

See Table 14.7 for antimycobacterial regimens.

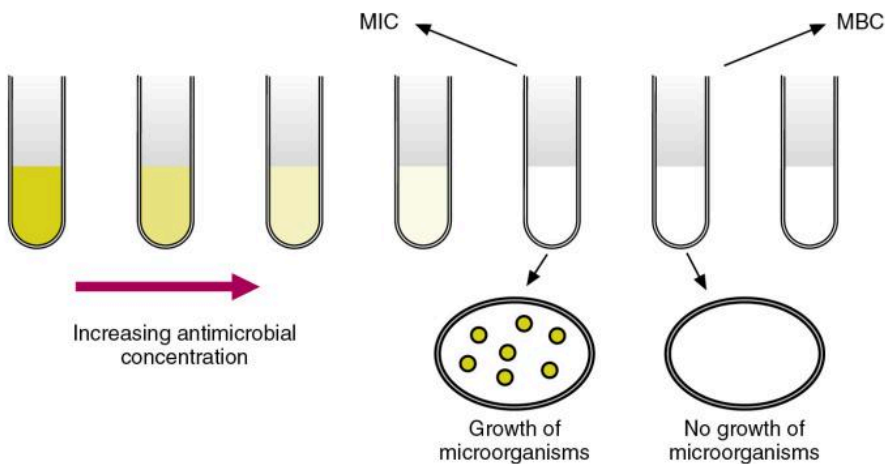
HIV, Human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus; TMP-SMX, trimethoprim-sulfamethoxazole.

Dickinson, Franklin Lakes, New Jersey), take advantage of broth microdilution methods for efficient and rapid provision of susceptibility results. When susceptibility testing is performed in broth media, a small sample can be removed from the test tubes or microwells with no growth and used to inoculate agar plates. The lowest concentration of antimicrobial agent that prevents growth of the organism on the agar plate after 24 hours of incubation is termed the minimal bactericidal concentration (MBC).³ Most laboratories do not routinely perform MBC testing, which is performed in specialized laboratories. They are often employed in research studies of new or investigational antimicrobial agents to determine whether these drugs are bacteriostatic or bactericidal. Drugs that inhibit the growth of bacteria but do not kill them are termed *bacteriostatic*. A bactericidal drug is one that kills the bacteria.^{3,5} Examples of bacteriostatic and bactericidal drugs are listed in Box 14.1.

Susceptibility testing is a crucial part of antimicrobial therapy because the empiric regimen may fail when used to treat infections with resistant organisms.² Microorganisms have genetic variability that affects their susceptibility to antimicrobials. Selective pressure from extensive clinical and agricultural use of antibiotics is thought to play an important role in the emergence of resistant bacteria.⁶ Mechanisms of bacterial resistance include the production of enzymes that degrade or modify antibiotics; the alteration of bacterial cell walls or membranes, resulting in decreased permeability; upregulation of antimicrobial efflux pumps; and alteration of the target site of antimicrobial action.⁶ Table 14.2 lists important emerging resistant bacteria.



• **Fig. 14.1** Disk diffusion test and E-test methods.



• **Fig. 14.2** Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) by broth microdilution.

Host Factors

KEY POINT

The outcome of antimicrobial therapy depends on host factors, the pathogen's susceptibility or resistance to the antimicrobial, and the pharmacodynamics of the antimicrobial.

Host factors play a significant role in the selection of optimal antimicrobial therapies. Consideration must be given to factors such as history of allergy or intolerance, age, organ dysfunction, pregnancy and lactation, and site of infection. Other important factors include immune status, travel history, recent exposure (approximately 3 months) to antimicrobials, as well as concomitant drugs

• BOX 14.1 Examples of Bactericidal/Fungicidal and Bacteriostatic/Fungistatic Antimicrobials

"Cidal"

- Aminoglycosides
- Carbapenems
- Cephalosporins
- Colistin
- Daptomycin
- Isoniazid
- Metronidazole
- Penicillins
- Polyenes
- Fluoroquinolones
- Rifampin, rifabutin
- Vancomycin*

"Static"

- Azoles
- Chloramphenicol
- Clindamycin
- Linezolid*
- Macrolides, azalides, ketolides
- Nitrofurantoin
- Quinupristin/dalfopristin*
- Tetracyclines
- Tigecycline
- Trimethoprim-sulfamethoxazole

*Agents that are bactericidal against *Staphylococcus aureus* but bacteriostatic against *Enterococcus* species.

TABLE 14.2 Emerging Resistant Bacterial Pathogens

Class of Bacteria	Name
Gram positive	MRSA
	VISA
	VRSA
	Penicillin-resistant <i>Streptococcus pneumoniae</i>
	VRE
Gram negative	MDR nonenteric bacilli (<i>Pseudomonas aeruginosa</i> , <i>Stenotrophomonas maltophilia</i> , <i>Acinetobacter</i> spp.)
	Third-generation cephalosporin-resistant <i>Enterobacter</i> and <i>Citrobacter</i> spp.
	ESBL-producing <i>Escherichia coli</i> and <i>Klebsiella</i> spp.
	Ampicillin-resistant <i>Haemophilus</i> spp.
	Carbapenemase-producing Enterobacteriaceae and <i>Acinetobacter</i> spp.

ESBL, Extended-spectrum β -lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VISA, vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *S. aureus*.

and disease states. In addition, drug factors, such as available dosage forms, ease of administration, pharmacokinetic and pharmacodynamic properties, tissue penetration, drug toxicities, and cost, influence the choice of a specific agent.⁴⁻⁶

The safety and efficacy of an antimicrobial agent varies, depending on the population of patients being treated.^{4,6} For example, bone marrow transplant recipients with an active infection may not improve despite use of the ideal antimicrobial agent because of their impaired immune function. Similarly, other immunocompromised hosts, such as patients with acquired immunodeficiency syndrome (AIDS), recipients of cancer chemotherapy or steroids, solid organ transplant recipients, and patients with diabetes, are also at risk of failing to improve on a regimen of antimicrobial therapy.⁶ Patients with infections involving foreign bodies or necrotic tissue often require surgical removal of the foreign device or necrotic tissue despite appropriate antimicrobial therapy. Other factors, such as altered pharmacokinetics of an antimicrobial, can affect response to therapy. For example, the absorption of certain antimicrobials, such as itraconazole (an antifungal agent), is increased in the presence of gastric acid; others, such as benzylpenicillin (penicillin G), are degraded in the presence of acid. The pH of the stomach varies with age; older patients tend to have achlorhydria, and young children tend to have a higher gastric pH. As a result, these two populations may have enhanced absorption of penicillin and decreased absorption of itraconazole compared with the rest of the population.

The function of the liver and the kidney also changes with age. These two organs play a major role in the metabolism and elimination of drugs from the body. Premature and newborn infants have diminished renal function at birth. Drugs that are eliminated unchanged in urine, such as β -lactams and aminoglycosides, require less frequent application because of their reduced clearance. Similarly, renal function declines with age, necessitating dosage reductions in older patients to prevent potential toxicities from antimicrobial accumulation.⁴⁻⁶

Prevention of toxicity to the fetus or infant while treating a pregnant or nursing mother is also a crucial consideration.^{4,6} Generally most β -lactams and macrolides are believed to be safe in pregnancy. The teratogenic potential of most other antimicrobials is unknown. However, tetracyclines have been shown to affect fetal dentition and to affect pregnant women adversely.⁴ Antimicrobials are often eliminated in breast milk and so have the potential to affect nursing infants adversely. For example, premature infants often have jaundice at birth because they are unable to conjugate and eliminate bilirubin efficiently. Even a small dose of sulfonamides ingested through breast milk from a treated mother can displace the albumin-bound bilirubin and predispose the infant to kernicterus. Kernicterus is marked by a pattern of cerebral palsy with uncoordinated movements, deafness, disturbed vision, and speech difficulties resulting from deposition of bilirubin in the developing brain.

Antimicrobials concentrate in varying degrees within organ systems and can influence the outcome of therapy.^{4,6} Clindamycin achieves excellent bone concentrations and is very useful for treatment of osteomyelitis resulting from susceptible organisms. Similarly, some drugs, such as aminoglycosides, most fluoroquinolones, and penicillins, achieve very high concentrations in urine and are useful for the treatment of urinary tract infections (UTIs). Conversely, certain drugs, although active against the organism in vitro, cannot achieve adequate concentrations at the site of infection. For example, aminoglycosides cannot penetrate the blood–brain barrier to treat meningitis adequately in adults. The blood–brain barrier represents tight junctions between the epithelial cells of the capillary wall that prevent drugs from entering the central nervous system.⁶

Some antimicrobials are not clinically effective at certain infection sites. Daptomycin, which has excellent in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA), is not effective for treatment of pneumonia because it is inactivated by lung surfactant.⁴ Aminoglycosides are less effective in low-oxygen, low-pH environments, such as abscesses. Drainage remains the most effective treatment for abscesses.⁴

Pharmacodynamics

Pharmacodynamics refers to the science of understanding the optimal effect of a drug as a function of its concentration and the in vitro activity (MIC) against an organism. The pharmacodynamic properties of an antimicrobial are measured in vitro by using time-kill studies. Time-kill tests are not performed in most microbiology laboratories but are performed in research facilities that study optimal dosages of antimicrobial agents. These studies measure the rate and extent of microorganism killing over time when exposed to varying concentrations of antimicrobials.³ If the microbial kill rate increases proportionally with drug concentration, the antimicrobial is said to have a concentration-dependent effect. If the microbial kill rate is influenced by the time of drug concentration above the MIC, the antimicrobial is defined as time dependent (or concentration independent).^{5,6} Another pharmacodynamic phenomenon exhibited by antimicrobials is known as the postantibiotic effect (PAE). The PAE refers to the sustained suppression of bacterial growth even after the concentration of the antibiotic declines below detectable levels. The length of the PAE varies according to the type of organism or drug. Generally, time-dependent drugs, such as β -lactams and vancomycin, have short PAEs, whereas concentration-dependent drugs, such as aminoglycosides, metronidazole, and fluoroquinolones, have longer PAEs. Agents with a short PAE should be given frequently, and longer intervals should be used for antimicrobials with a long PAE. These

pharmacodynamic properties have been shown in vitro and in numerous animal studies.⁶ Clinical trials validating these principles are ongoing, and practical guidelines to incorporate pharmacodynamics in clinical practice have been published, resulting in increased use of extended infusions for piperacillin-tazobactam and carbapenems.

Antimicrobial Combinations

Empiric regimens must often cover a broad spectrum of organisms, which occasionally requires the use of two or more classes of antimicrobials. Ideally, the regimen should be narrowed after the specific organism has been isolated and susceptibilities are determined. Certain infections are polymicrobial, and in certain settings, the use of antimicrobial combinations is justified. When antimicrobials are used in combination, it is important to know whether these agents act synergistically or antagonistically.^{5,6} **Synergy** is shown in vitro when the combined effect of two antimicrobials is greater than the sum of their individual effects. Synergistic combinations have played a vital role in the treatment of resistant *Pseudomonas* infections in patients with cystic fibrosis (CF). These patients have recurrent bouts of pseudomonal pneumonia and are often colonized with resistant species. Certain synergistic combinations of β -lactams and aminoglycosides have been shown to curb the development of resistance and to improve outcomes.^{5,6} **Antagonism** occurs when the effect of the combined drugs is lower than the sum of their independent activities when measured separately.⁴ Antagonism may result in an unfavorable response, and such drug combinations should be avoided. A classic example of antagonism was the use of tetracycline (static) and penicillin (cidal) in children with pneumococcal meningitis. The rate of mortality associated with the use of combination therapy was three times higher than that with the use of penicillin alone. However, not all combinations of static and cidal antimicrobials are detrimental. Ceftriaxone (cidal) and a static agent, such as a macrolide, azalide, or tetracycline, are considered drugs of choice for CAP.⁷

Monitoring Response to Therapy

CLINICAL CONNECTION

Treatment failure may manifest as continued fever spikes, elevated white blood cell (WBC) count, repeated positive cultures, and nonresolution of symptoms.

Certain laboratory parameters can be monitored to assess the efficacy of an antimicrobial regimen, but ultimately the clinical assessment of the patient is the best measure of response to therapy. Treatment failure may manifest as continued fever spikes, elevated white blood cell (WBC) count, repeated positive cultures, or nonresolution of symptoms (shortness of breath, cough, sputum production).⁶ The reasons for failure can be multifactorial and require consideration of all the aforementioned factors. In addition, noncompliance with the treatment regimen can play a significant role in outpatient treatment failures.

The use of antimicrobials can be associated with significant toxicities. The agent amphotericin B, which is used to treat fungal infections, such as pulmonary aspergillosis, can cause significant renal dysfunction. Aminoglycosides can also cause renal dysfunction. Serum concentrations of aminoglycosides are routinely monitored to ensure therapeutic, but nontoxic levels.⁶ Similarly, other agents can have adverse effects on the liver, gastrointestinal tract,

neuromuscular system, hematologic system, heart, and lungs. The incidence of these adverse events varies among agents and is often reversible. Careful monitoring of patients receiving antimicrobials can prevent serious and potentially life-threatening adverse events.

Antibiotics

Numerous **antibiotics**, substances derived or produced from a microorganism that inhibit or kill other microorganisms, are available to treat infectious diseases. A synopsis of the mechanism of action, clinical uses, and adverse reactions of each class is provided in the following sections.

Penicillins

KEY POINT

The β -lactams are a large class of antibiotics that includes penicillins, cephalosporins, carbapenems, and monobactams (aztreonam).

The discovery of penicillin in 1928 by Fleming ultimately led to the creation of a broad class of antibiotics commonly referred to as β -lactams. β -lactam antibiotics include penicillins, cephalosporins, monobactams, and carbapenems.^{10,11} The main constituent of these antibiotics is the β -lactam ring structure. Chemical manipulation of β -lactam side chains led to the development of new agents with enhanced spectra of antimicrobial activity compared with penicillin. Specific side-chain modifications of penicillin have resulted in a broad class that includes the natural penicillins, aminopenicillins, penicillinase-resistant penicillins, carboxypenicillins, and ureidopenicillins (Table 14.3). Penicillins have also been combined with β -lactamase inhibitors to overcome a common mechanism of bacterial resistance.

Penicillins generally are widely distributed throughout the body and are associated with relatively low levels of toxicity. Most penicillins are acid labile (destroyed in the stomach) and therefore are poorly absorbed after oral administration. Most agents in this class are not metabolized but are excreted unchanged in urine. Therefore, most penicillins require reductions in dosage for patients with renal dysfunction.^{10,11}

Mechanism of Action

Penicillins exert their pharmacologic activity by inhibiting cell wall synthesis. Penicillins bind to enzymes (penicillin-binding proteins) located within the cell wall and prevent cross-linking of the peptidoglycan structure necessary for cell wall development. In addition, penicillins activate an endogenous autolytic system within bacteria, which subsequently leads to cell lysis and death. Penicillins are bactericidal, exhibit time-dependent killing, and act synergistically with aminoglycosides against some bacteria (i.e., *P. aeruginosa* and enterococci).^{10,11}

Clinical Uses

Natural Penicillins. Penicillin G is the parent compound of this class. Natural penicillins are effective primarily against gram-positive bacteria and anaerobes. Penicillin G is the drug of choice for the treatment of primary and secondary syphilis (*Treponema pallidum*), along with pharyngitis caused by group A streptococci (*Streptococcus pyogenes*). Because of the increasing frequency of resistance in *S. aureus*, *S. pneumoniae*, and *Neisseria gonorrhoeae*, penicillin G should no longer be considered for infections caused by these organisms.^{10,11}

TABLE 14.3 Classification and Clinical Uses of Penicillins^{10–15}

β -Lactam Class (Generic Name)	Brand Name	Route	Common Uses (Microorganism)
Natural Penicillins			
Penicillin G (potassium)	Pfizerpen	IM, IV	<i>Streptococcus pyogenes</i> , <i>Neisseria meningitidis</i> , <i>Bacillus anthracis</i> (anthrax), <i>Clostridioides perfringens</i> (gangrene), <i>Pasteurella multocida</i> , <i>Treponema pallidum</i> (syphilis)
Penicillin G (procaine)	Wycillin	IM	
Penicillin G (benzathine)	Bicillin L-A	IM	
Penicillin V (potassium)	Pen-Vee K	PO	
Penicillinase-Resistant Penicillins			
Oxacillin	Prostaphlin	PO, IM, IV	MSSA, MSSE
Nafcillin	Unipen	IV	
Dicloxacillin	Dynapen	PO	
Aminopenicillins			
Ampicillin	Omnipen	PO, IM, IV	<i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Eikenella corrodens</i> , <i>Borrelia burgdorferi</i> , <i>Haemophilus influenzae</i> , <i>Escherichia coli</i>
Amoxicillin	Amoxil, Wymox	PO	
Ureidopenicillins			
Piperacillin	Pipracil	IM, IV	<i>Pseudomonas aeruginosa</i> , <i>Enterobacteriaceae</i> , <i>Stenotrophomonas</i> spp.
Penicillin Plus β-Lactamase Inhibitors			
Amoxicillin–clavulanic acid Ampicillin-sulbactam	Augmentin, Unasyn	PO, IM, IV	Increased activity against β -lactamase–producing strains <i>S. aureus</i> , <i>H. influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Proteus</i> spp., <i>Bacteroides</i> spp.
Piperacillin-tazobactam	Zosyn	IV	<i>P. aeruginosa</i> , <i>Enterobacteriaceae</i>
<i>IM</i> , Intramuscular; <i>IV</i> , intravenous; <i>MSSA</i> , methicillin-sensitive <i>Staphylococcus aureus</i> ; <i>MSSE</i> , methicillin-sensitive <i>Staphylococcus epidermidis</i> ; <i>MRSA</i> , methicillin-resistant <i>Staphylococcus aureus</i> ; <i>PO</i> , oral.			

IM, Intramuscular; IV, intravenous; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral.

Penicillinase-Resistant Penicillins. In an attempt to overcome the emergence of penicillinase-producing (β -lactamase–producing) staphylococci, semisynthetic penicillinase-resistant antibiotics were developed. These agents are commonly referred to as antistaphylococcal agents because of their excellent activity against *S. aureus*. Methicillin was the first agent in this class of antibiotics, followed by oxacillin, nafcillin, cloxacillin, and dicloxacillin. Chemical modification of penicillin by the addition of an acyl side chain prevents hydrolysis of the agents in the presence of penicillinase. This class has activity against gram-positive cocci (staphylococci and streptococci) and is routinely used in skin and soft tissue infections. These agents are ineffective in the treatment of infections caused by gram-negative organisms or anaerobes. Until the 1980s, these antibiotics were the mainstay of treatment against staphylococci. However, the emergence of methicillin-resistant staphylococci has greatly reduced the clinical effectiveness of these agents.^{10,11}

Aminopenicillins. Aminopenicillins were the first penicillin class developed that were considered clinically active against some gram-negative bacteria (*E. coli*, *H. influenzae*). Ampicillin and amoxicillin are the primary antibiotics in this class. In contrast to penicillin, ampicillin and amoxicillin are stable in gastric acid and therefore are suitable for oral administration. Both ampicillin and amoxicillin are frequently used in infections with susceptible

organisms of the respiratory (*S. pneumoniae*, *H. influenzae*) and urinary (*E. coli*) tracts.^{10,11}

Carboxypenicillins. Carbenicillin was the first penicillin to have activity against *P. aeruginosa*. It was also active against most members of the family Enterobacteriaceae, including *E. coli*, *Enterobacter*, *Proteus*, *Morganella*, and *Serratia*. Subsequent modification of carbenicillin resulted in ticarcillin, which has even greater in vitro activity against *P. aeruginosa* and members of Enterobacteriaceae (including *Klebsiella*). Neither of these agents is considered to have appreciable activity against gram-positive organisms (staphylococci or streptococci). Because of the subsequent development of the ureidopenicillins, carboxypenicillins are rarely used in clinical practice.^{10,11}

Ureidopenicillins. Although carbenicillin and ticarcillin provided increased gram-negative coverage, antimicrobial agents with enhanced antipseudomonal activity were still needed. The ureidopenicillins were developed to fill this need. Piperacillin is a penicillin antibiotic with enhanced gram-negative activity (especially against *P. aeruginosa*) and with fewer adverse reactions than carboxypenicillins. Ureidopenicillins also exhibit activity against streptococci and enterococci and many anaerobes. Piperacillin is the primary agent of this class and has been efficacious in the treatment of pneumonia, bacteremia, UTIs, osteomyelitis, and soft tissue infections.^{10,11}

β -Lactam and β -Lactamase Inhibitor Combinations. Certain bacteria have the ability to produce enzymes (β -lactamases) that destroy the activity of penicillins by disrupting the β -lactam structure. β -lactamase inhibitors were developed to overcome this form of resistance. Combination β -lactams and β -lactamase inhibitors have a large spectrum of activity, making them particularly useful in polymicrobial infections. At present, there are a number of β -lactamase inhibitors approved for combination with penicillins, cephalosporins and carbapenems: clavulanic acid, sulbactam, tazobactam, avibactam, relebactam, and vaborbactam.^{12–14} β -Lactamase inhibitors enhance the activity of β -lactams against β -lactamase-producing strains of *S. aureus*, *Moraxella catarrhalis*, *E. coli*, *H. influenzae*, *Klebsiella* species, and *Bacteroides* species.¹⁵ Newer combinations have enhanced activity against ESBL-producing isolates as well as some carbapenemase-producing isolates as seen with meropenem/vaborbactam and imipenem/cilastatin/relebactam.^{12–14}

Adverse Reactions and Precautions

The most common adverse reaction to penicillins is hypersensitivity. Approximately 3% to 10% of the population is allergic to penicillin. Reactions vary in severity from a mild rash to life-threatening anaphylaxis. Patients allergic to a penicillin could be potentially allergic to all classes of β -lactams (cephalosporins, carbapenems). In addition to allergic reactions, hematologic reactions, such as thrombocytopenia and increased bleeding times, have been reported. Gastrointestinal disturbances (nausea, vomiting, and diarrhea) are more common with oral dosage forms of penicillins, especially ampicillin. Interstitial nephritis has occurred most commonly with methicillin (not commercially available) but may occur with other penicillins as well. Central nervous system toxicities (e.g., seizures) have been reported with penicillins. Patients with an underlying seizure disorder and patients with renal insufficiency are at greatest risk for developing this complication.

Cephalosporins

KEY POINT

Cephalosporins have been loosely grouped into “generations” on the basis of their spectrum of activities. At present, there are five generations (classes) of cephalosporins.

Cephalosporins include a large group of antimicrobials that are structurally related to penicillins. Discovered in the 1940s as a microbial by-product of the fungus *Cephalosporium acremonium*, this class is now widely used in clinical practice. Similar to penicillins, this class exhibits bactericidal activity, is distributed throughout the body, and produces relatively few adverse effects. Cephalosporins are used for various clinical indications and are available in oral and intravenous formulations¹⁶ (Table 14.4). Agents from this class have been loosely grouped into “generations” on the basis of their spectrum of activities. At present, there are five generations (classes) of cephalosporins.

Mechanism of Action

Cephalosporins inhibit bacterial cell wall synthesis in a manner similar to penicillins. Cephalosporins bind to the penicillin-binding proteins within the cell wall and inhibit the cross-linking of peptidoglycan. This inhibition compromises the structural integrity of the bacterial cell wall, resulting in cell lysis (bactericidal).

Clinical Uses

CLINICAL CONNECTION

Many different agents are available in the classification. These agents are commonly used for their broad-spectrum capabilities. Ceftazone (Rocephin) is a frequently used agent in this classification.

As a class, cephalosporins are active against a wide variety of organisms. Because of their broad spectrum of activity and low level of toxicity, these agents are commonly used for a wide variety of infections. The spectrum of activity differs for each cephalosporin generation. All cephalosporins are ineffective against enterococci.¹⁶

First-Generation Cephalosporins. First-generation cephalosporin agents are very active against a wide variety of gram-positive organisms, including methicillin-sensitive *S. aureus* (MSSA) and streptococci. They have moderate activity against community-acquired, gram-negative organisms such as *E. coli*, *Klebsiella pneumoniae*, *H. influenzae*, *M. catarrhalis*, and some *Proteus* species. They are also considered effective against many oral anaerobes (e.g., *Peptostreptococcus*). Commonly used agents within this class are cephalexin, cefazolin, and cefadroxil. These agents are not active against *Bacteroides fragilis*, *P. aeruginosa*, and most members of Enterobacteriaceae. Generally, first-generation cephalosporins are appropriate for treatment of infections of skin and soft tissue, uncomplicated community-acquired UTIs, streptococcal pharyngitis, and surgical prophylaxis.¹⁶

Second-Generation Cephalosporins. Second-generation cephalosporins comprise two groups: true cephalosporins and synthetic cephamycins. Cefuroxime, cefprozil, and cefaclor are among the more widely used true cephalosporins. In contrast to first-generation cephalosporins, these agents display enhanced gram-negative activity and maintain comparable gram-positive activity. This group provides improved activity against *H. influenzae*, *M. catarrhalis*, *Neisseria meningitidis*, *N. gonorrhoeae*, and some members of Enterobacteriaceae. These agents are considered effective in treating CAP, otitis media, pharyngitis, skin and soft tissue infections, and uncomplicated UTIs.¹⁶

Cephameycins, consisting of cefotetan and cefoxitin, have enhanced activity against gram-negative members of Enterobacteriaceae and anaerobic activity against many *Bacteroides* species. They are not considered effective against gram-positive organisms, such as staphylococci and streptococci. Cephameycins are also useful in the treatment of intraabdominal, pelvic, and gynecologic infections; decubitus ulcers; diabetic foot syndrome; and mixed aerobic-anaerobic soft tissue infections.¹⁶

Third-Generation Cephalosporins. Commonly used third-generation cephalosporins are cefixime, cefpodoxime, ceftibuten, cefdinir, cefotaxime, ceftazidime, ceftriaxone, and ceftizoxime. These agents are active against most gram-negative organisms. However, only ceftazidime and to a lesser extent cefoperazone have activity against *P. aeruginosa*. Third-generation cephalosporins show excellent activity against *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *N. meningitidis*, *N. gonorrhoeae*, and *M. catarrhalis*. Although activity varies with individual agents, this group is not considered to have significant activity against anaerobes. Ceftriaxone, cefotaxime, and to a lesser extent ceftizoxime achieve clinically significant concentrations within the meninges, making them ideal agents for the treatment of meningitis. In addition, ceftriaxone has replaced penicillin as the agent of choice in treating all forms of gonococcal (*N. gonorrhoeae*) infection resulting

TABLE 14.4 Classification and Clinical Uses of Cephalosporins^{16–21}

Cephalosporin (Generic Name)	Brand Name	Route	Common Uses (Microorganism)
First Generation			
Cefadroxil	Duricef	PO	MSSA, streptococci
Cephalexin	Keflex, Biocef	PO	
Cefazolin	Ancef, Kefzol	IM, IV	
Second Generation			
Cefaclor	Ceclor	PO	MSSA, MSSE, <i>Streptococcus pneumoniae</i> , <i>Klebsiella</i> spp., <i>Escherichia coli</i> , <i>Proteus</i> spp., <i>Haemophilus influenzae</i>
Cefprozil	Cefzil	PO	
Cefuroxime axetil	Ceftin	PO	
Cefuroxime	Zinacef, Kefurox	IM, IV	
Cefotetan	Cefotan	IM, IV	As above plus <i>Bacteroides fragilis</i>
Cefoxitin	Mefoxin	IM, IV	
Third Generation			
Cefixime Cefpodoxime proxetil	Suprax, Vantin	PO PO	Better activity than second-generation cephalosporins against <i>Klebsiella</i> , <i>E. coli</i> , <i>Proteus</i> spp., <i>H. influenzae</i> , <i>Enterobacter</i> spp.
Ceftibuten	Cedax	PO	
Cefdinir	Omnicef	PO	
Cefotaxime	Claforan	IM, IV	
Ceftriaxone	Rocephin	IM, IV	
Ceftizoxime	Cefizox	IM, IV	
Ceftazidime	Fortaz, Tazidime	IM, IV	As above plus <i>Pseudomonas aeruginosa</i>
Ceftazidime-avibactam	Avycaz	IV	Avycaz also has activity against <i>K. pneumoniae</i> carbapenemase-producing organisms
Cefoperazone	Cefobid	IM, IV	
Ceftolozane-tazobactam	Zerbaxa	IV	<i>Enterobacter cloacae</i> , <i>E. coli</i> , <i>Klebsiella</i> spp., <i>P. mirabilis</i> , <i>Pseudomonas aeruginosa</i> , <i>S. anginosus</i> , <i>S. constellatus</i> , <i>S. salivarius</i> , and <i>B. fragilis</i>
Fourth Generation			
Cefepime	Maxipime	IM, IV	MSSA, <i>S. pneumoniae</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>Proteus</i> spp., <i>H. influenzae</i> , <i>P. aeruginosa</i> , <i>Enterobacter</i> spp.
Fifth Generation			
Ceftaroline	Teflaro	IM, IV	MRSA, <i>S. pneumoniae</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>Proteus</i> spp., <i>H. influenzae</i> , <i>Enterobacter</i> spp.

IM, Intramuscular; IV, intravenous; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral.

from the increased prevalence of β -lactamase-producing strains. Third-generation cephalosporins are commonly used to treat nosocomial pneumonia, bacteremia, UTIs, osteomyelitis, and soft tissue infections. The most recent third-generation cephalosporins to be developed are the cephalosporin/ β -lactamase inhibitor combinations—ceftolozane/tazobactam (Zerbaxa) and ceftazidime/avibactam (Avycaz). Ceftolozane/tazobactam is active against most gram-negative bacteria with some activity against gram-positive organisms (*S. anginosus*, *S. constellatus*, and *S. salivarius*). Ceftazidime/avibactam possesses the same spectrum of activity as ceftazidime. Combination third-generation cephalosporins allow these agents to maintain antimicrobial activity in the presence of select

extended-spectrum β -lactamases (ESBLs) and some other clinically relevant β -lactamase-producing organisms. These agents are reserved for the treatment of complicated intraabdominal infections, UTIs, and other infections caused by resistant β -lactamase-producing organisms.^{16,17}

Fourth-Generation Cephalosporins. Fourth-generation cephalosporins offer extended gram-positive and gram-negative coverage. Cefepime is presently the only agent available in the United States. It is parentally administered and active against most gram-negative aerobic organisms, including *P. aeruginosa*. In addition, it has excellent activity against MSSA, *Neisseria* species, *H. influenzae*, *S. pneumoniae*, and *S. pyogenes*. Cefepime has been used primarily in the

treatment of uncomplicated and complicated UTIs and skin and soft tissue infections, as well as in empiric treatment of neutropenic fever, nosocomial pneumonia, and other serious bacterial infections.^{16,18}

Fifth-Generation Cephalosporins. Ceftriaxone is the first and only member of the latest class of cephalosporins. Similar to fourth-generation cephalosporins, it has broad gram-negative and gram-positive activity. Unlike cefepime, ceftriaxone has activity against MRSA but is inactive against *P. aeruginosa*. It is approved for use in CAP, as well as skin and skin structure infections. It appears to have a role in treating various types of polymicrobial infections, especially those by MRSA.^{18,19}

Adverse Reactions and Precautions

Similar to penicillins, cephalosporins as a group are well tolerated. Hypersensitivity reactions occur in 1% to 3% of patients, with cross-reactivity of cephalosporins in patients with penicillin allergy ranging from 5% to 15%. Generally, patients with a penicillin allergy (limited to a rash) may be challenged with a cephalosporin. Cephalosporin use is contraindicated, however, in patients with a history of anaphylaxis to β -lactams. Desensitization should be performed if no therapeutic alternative exists for the use of a cephalosporin.²⁰ Oral cephalosporins have been associated with minor gastrointestinal complaints, such as nausea, vomiting, and diarrhea. Hypoprothrombinemia has been reported, especially with agents (cefotetan and cefoperazone) with a methylthiotetrazole (MTT) side chain. The MTT side chain may also induce a disulfiram-like reaction in patients who concurrently ingest alcohol (disulfiram inhibits the metabolism of alcohol). The symptoms of this uncomfortable reaction include flushing, nausea, thirst, palpitations, chest pain, vertigo, and death in some cases. Most cephalosporins are eliminated through the kidneys and require dosage adjustment in the presence of renal insufficiency.²¹

Carbapenems

Carbapenems are the newest class of β -lactam antibiotics. At present three carbapenems—imipenem-cilastatin, meropenem, and ertapenem—are available for use in the United States. Cilastatin is used to inhibit the metabolism of imipenem within the kidney to prolong the half-life of this agent. Carbapenems are broad-spectrum antibiotics, displaying activity against a wide variety of gram-positive, gram-negative, and anaerobic bacteria.^{22–24}

Mechanism of Action

The mechanism of action of carbapenems is similar to other β -lactam antibiotics. These agents demonstrate bactericidal activity.

Clinical Uses

Imipenem and meropenem, are active against *P. aeruginosa*, multidrug-resistant (MDR) gram-negative bacilli, and most anaerobes. Meropenem also exists as a combination with vaborbactam (Vabomere), a potent β -lactamase inhibitor with activity against *K. pneumoniae* carbapenemases (KPCs). Ertapenem differs from other carbapenems in that it possesses no activity against *P. aeruginosa*. All four carbapenems have activity against gram-positive organisms, such as MSSA and the *Streptococcus* species, including pneumococci (*S. pneumoniae*). Imipenem and meropenem have been used clinically for empiric treatment of bacteremia and sepsis, CAP and nosocomial pneumonia, skin and skin structure infections, complicated UTIs, intraabdominal infections, obstetric and gynecologic infections, osteomyelitis, and infections in patients with cancer and neutropenia. Because ertapenem is

ineffective against *P. aeruginosa*, it should not be used in the treatment of nosocomial pneumonia, neutropenic fever, or any other infection in which *P. aeruginosa* is a likely pathogen. Because of their excellent in vitro activity and broad spectrum of coverage, these agents are often reserved for treatment of infections that are caused by bacteria resistant to most other agents.^{22–25}

Adverse Reactions and Precautions

Carbapenems are generally well tolerated, with a low incidence of adverse reactions. Because carbapenems are structurally related to other β -lactam antibiotics, cross-reactivity may occur when they are used in patients with allergies to β -lactams. The occurrence of seizures has been reported with carbapenems, more frequently with imipenem than with meropenem, or ertapenem. Seizures are most commonly seen in patients with decreased renal function and patients with an underlying seizure disorder. Dosage adjustment is necessary in the presence of renal insufficiency to prevent accumulation of the drug and to reduce the potential for seizures.^{22–24}

Monobactams (Aztreonam)

Aztreonam is a synthetic monocyclic β -lactam antibiotic. It is the only commercially available agent belonging to the class of antibiotics known as *monobactams*.²⁴

Mechanism of Action

The mechanism of action of aztreonam is similar to other β -lactam antibiotics, and it also exhibits bactericidal activity.

Clinical Uses

CLINICAL CONNECTION

Aztreonam is approved by the US Food and Drug Administration (FDA) as an aerosol in the treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (see Chapter 13).

Aztreonam is active only against gram-negative aerobic bacilli (most Enterobacteriaceae and *P. aeruginosa*). It is ineffective against gram-positive and anaerobic bacteria. The strict gram-negative spectrum of aztreonam limits its use as a single agent. It has been used for the treatment of serious UTIs and bacteremia. Aztreonam has more extensive use in combination therapy for treatment of patients with intraabdominal infections, spontaneous bacterial peritonitis, gram-negative osteomyelitis, HAP, and neutropenic fever.²⁴

Adverse Reactions and Precautions

Aztreonam is well tolerated and is thought to have little to no cross-reactivity to β -lactams. Rare cases of rashes and anaphylactic reactions have been reported when aztreonam was used in patients with a β -lactam allergy.²⁴

Aminoglycosides

Streptomycin was discovered in 1943 and was the first antimicrobial agent available for the treatment of tuberculosis. Numerous other aminoglycosides have been developed since and include gentamicin, tobramycin, netilmicin, and amikacin. These agents are used for treating gram-negative infections, including infections caused by *P. aeruginosa*. These antimicrobials have poor gastrointestinal absorption and require parenteral administration.²⁶ Table 14.5 lists aminoglycosides and their clinical uses.

TABLE 14.5 Clinical Uses of Aminoglycosides^{26–29}

Generic Name (Trade Name)	Brand Name	Most Common Clinical Uses*
Streptomycin		Brucellosis, tuberculosis, endocarditis caused by gentamicin-resistant enterococci
Gentamicin	Garamycin	Nosocomial Enterobacteriaceae and <i>Pseudomonas aeruginosa</i> infections, tularemia, brucellosis; endocarditis caused by susceptible enterococci or viridans streptococci, <i>Staphylococcus aureus</i> , <i>Corynebacterium</i> spp., penicillin-susceptible <i>Streptococcus</i>
Tobramycin	Nebcin	
Amikacin	Amikin	Similar to gentamicin and tobramycin but useful against <i>Acinetobacter</i> spp., <i>Nocardia</i> spp., <i>Mycobacterium avium-intracellulare</i> , <i>Mycobacterium chelonae</i> , <i>Mycobacterium fortuitum</i>

*The aminoglycosides (most commonly gentamicin and tobramycin) are used to treat infections caused by gram-negative bacteria.

Mechanism of Action

Aminoglycosides bind irreversibly to the 30S bacterial ribosome and inhibit the translation of RNA into proteins. Aminoglycosides also competitively displace cations that link lipopolysaccharides in the outer cell wall of gram-negative bacteria. This destabilization of the cell wall results in increased cell permeability and lysis. Aminoglycosides are bactericidal agents and exhibit concentration-dependent killing. They are often synergistic when used in combination with β -lactam antibiotics.^{26–29}

Clinical Uses

CLINICAL CONNECTION

Tobramycin is approved by the US Food and Drug Administration (FDA) as an aerosol for the treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (see Chapter 13).

Gentamicin, tobramycin, and amikacin all have been used for nosocomial gram-negative infections, such as VAPs. However, aminoglycosides do not achieve high concentrations in bronchial secretions when administered systemically; this is thought to be particularly problematic for patients infected by resistant gram-negative organisms. As a result, aminoglycosides (particularly tobramycin and now amikacin) have been administered by inhalation to control *P. aeruginosa* infections in patients with CF (see Chapter 13). Amikacin is currently more expensive and is generally reserved for organisms resistant to other aminoglycosides. Aminoglycosides are used synergistically with β -lactams when treating endocarditis caused by the *Streptococcus* species and *Enterococcus* species. Aminoglycosides are also used extensively to treat intraabdominal infections. Streptomycin is used in combination with other antitubercular antimicrobials, especially for MDR tuberculosis.^{26–29}

Adverse Reactions and Precautions

KEY POINT

Primary toxicities associated with the use of aminoglycosides are nephrotoxicity and ototoxicity.

The primary toxicities associated with the use of aminoglycosides are nephrotoxicity and ototoxicity. Nephrotoxicity usually develops after at least 5 to 7 days of therapy and occurs more commonly in patients with hypotension, liver disease, advanced age,

and coadministration of other nephrotoxic agents. Ototoxicity (both cochlear toxicity and vestibular toxicity) may be irreversible because significant damage must occur before it can be detected. The most common symptoms associated with the development of cochlear toxicity include tinnitus (ringing in the ears); vestibular toxicity manifests as dizziness and nausea. Another serious but rare toxicity is neuromuscular blockade associated with peritoneal irrigation and rapid high-dose aminoglycoside use. Underlying conditions, such as myasthenia gravis, or concomitant use of neuromuscular blockers may potentiate this side effect, requiring supportive measures, such as intubation and potential ventilation support.^{26–29}

Tetracyclines

CLINICAL CONNECTION

Tetracyclines are broad-spectrum antibiotics with activity against gram-positive and gram-negative microorganisms and many rickettsiae, chlamydia, mycoplasmas, spirochetes, protozoa, and mycobacteria.

Tetracyclines are broad-spectrum antibiotics with activity against gram-positive and gram-negative microorganisms and many rickettsiae, chlamydia, mycoplasmas, spirochetes, protozoa, and mycobacteria. The most commonly used agent in this class is doxycycline because it can be administered twice daily and is relatively inexpensive. Other available tetracyclines include minocycline and tetracycline. The agents are available in oral and parenteral formulations.³⁰

Mechanism of Action

Tetracyclines bind reversibly on the 30S ribosome and inhibit the attachment of transfer RNA to an acceptor site on the messenger RNA-ribosome complex. This inhibition blocks protein synthesis and results in a bacteriostatic effect.

Clinical Uses

Clinical conditions in which tetracyclines are used include respiratory tract infections and other systemic infections. Acute exacerbation of chronic bronchitis (AECB) and CAP caused by typical (*S. pneumoniae*, *H. influenzae*) and atypical (*C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*) bacteria can be treated with a tetracycline. Tetracyclines are also useful for the treatment of *Chlamydia trachomatis* infection (a sexually transmitted disease), Rocky Mountain spotted fever, Q fever, typhus, brucellosis, Lyme

disease, ehrlichiosis, relapsing fever, and cholera. Tetracyclines tend to concentrate in the skin and are useful for the treatment of acne. Tetracyclines have also been used as sclerosing agents for the treatment of malignant and refractory pleural effusions.³⁰

Adverse Reactions and Precautions

Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, are the most common side effects associated with tetracyclines. Tetracyclines bind to growing bone and can temporarily inhibit their growth. Because of the latter side effect, use of tetracyclines is contraindicated in women during pregnancy and breastfeeding and in children younger than 8 years of age. Tetracyclines bind to divalent and trivalent cations (calcium, magnesium, aluminum, and iron), which decreases their gastrointestinal absorption when given with antacids, iron supplements, and dairy products. Avoiding the coadministration of tetracyclines with these agents by 1 to 2 hours can prevent this interaction.³⁰

Tetracycline Derivatives

Tigecycline, eravacycline and omadacycline are structural derivative of tetracycline.^{31–34} Like tetracycline antibiotics, these agents all contain a central four-ring carbocyclic nucleus, with eravacycline containing a fluorine atom, at the C-7 position, along with a glyclamido group at the C-9 position as similarly seen in tigecycline. Omadacycline is structurally similar to tigecycline without the substitution at C-9. All three of these agents have a greater spectrum of activity than other tetracyclines. Tigecycline, eravacycline, and omadacycline are active against most gram-positive bacteria, including *S. pneumoniae*, enterococci (including vancomycin-resistant strains), coagulase-negative staphylococci, MSSA, MRSA, *H. influenzae*, *M. catarrhalis*, most members of the Enterobacteriaceae family (including ESBL-producing organisms), and *Acinetobacter* species. They also appear active against isolates possessing common tetracycline resistance observed at the efflux pumps and ribosomal binding proteins. They are also active against many anaerobic bacteria; however, none of the three agents display clinical significant activity against *P. aeruginosa* and *Proteus* species.^{31–33}

Mechanism of Action

Tigecycline, eravacycline, and omadacycline display a similar mechanism of action to tetracycline antibiotics by inhibiting bacterial protein synthesis at the 30S ribosome. Because of the large, bulky constituent at ring position 9, along with other modifications, they maintain antimicrobial activity against organisms that carry resistance to tetracycline antibiotics. Similar to tetracycline, they are generally considered to be bacteriostatic against most organisms except *S. pneumoniae*, to which it is bactericidal.^{33,34}

Clinical Uses

Tigecycline is currently approved for the treatment of complicated skin and skin structure infections, complicated intraabdominal infections, and bacterial CAP. Omadacycline is approved for CAP and complicated skin and skin structure infection, whereas eravacycline is approved for complicated intraabdominal infections. Of note, the US Food and Drug Administration (FDA) recommends using alternatives to tigecycline to treat severe infections after a report of decreased cure rates and increased mortality in a study involving patients with VAP receiving tigecycline compared with imipenem.³⁴ The same would hold true for omadacycline and eravacycline as they do not have any appreciable activity against

Pseudomonas aeruginosa. Tigecycline and eravacycline are available only as an intravenous formulation, whereas omadacycline is available as an oral and IV formulation.

Adverse Reactions and Precautions

During clinical trials, the most common side effects observed were gastrointestinal and included nausea, vomiting, diarrhea, and abdominal pain, especially with tigecycline and omadacycline. Other frequently reported adverse effects were headache, thrombocytopenia, and elevations of liver enzymes. Because these agents are a structural derivative of minocycline, it is appropriate to monitor for side effects associated with other tetracycline antibiotics, such as phototoxicity and dental disorders. These agents should not be used in individuals with hypersensitivity reactions to tetracycline antibiotics.^{32,34}

Macrolides, Azalides, and Ketolides

KEY POINT

Macrolides, azalides, and ketolides exhibit activity against gram-positive bacteria (streptococci and MSSA), gram-negative bacteria (*H. influenzae*, *M. catarrhalis*), and atypical bacteria (mycoplasmas, rickettsiae, *Legionella*, and *Chlamydia*).

Erythromycin was the first agent of this class to be used for infections with atypical organisms and for infections in patients intolerant to penicillin G. Early work with erythromycin involved production of various salt derivatives to improve its gastrointestinal tolerability and absorption. Clarithromycin, azithromycin (an azalide), and telithromycin (a ketolide) were introduced in subsequent years. These agents exhibit activity against gram-positive bacteria (streptococci, MSSA), gram-negative bacteria (*H. influenzae*, *M. catarrhalis*), and atypical bacteria (mycoplasmas, rickettsiae, *Legionella*, and *Chlamydia*). Clarithromycin and azithromycin are also active against *Mycobacterium avium* and other mycobacterial species.³³

Mechanism of Action

Macrolides, azalides, and ketolides inhibit protein synthesis by reversibly binding to the 50S ribosomal subunit and induce the dissociation of transfer RNA from the ribosome during the elongation phase. As a result, bacterial growth is inhibited (bacteriostatic).

Clinical Uses

These agents are used for the treatment of pneumonia caused by the atypical pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Macrolides and azalides are considered a safer alternative to tetracyclines for the treatment of chlamydial (*C. trachomatis*) pelvic infections in pregnant women. Clarithromycin is the preferred agent in combination with ethambutol or rifabutin for the treatment of *M. avium* complex (MAC) in patients with human immunodeficiency virus (HIV) infection. Azithromycin has a superior pharmacokinetic profile compared with the latter agents because it maintains prolonged intracellular concentrations (long half-life). As a result, azithromycin can be administered once weekly for prophylaxis of MAC in patients with HIV, whereas clarithromycin must be administered twice daily. Similarly, 3-day and 5-day regimens of azithromycin have been found to be as effective as a 10-day regimen of erythromycin for the treatment of CAP.³³ Telithromycin was approved for the treatment of AECB,

acute bacterial sinusitis, and CAP. It may serve as an alternative agent for patients at risk of infection with penicillin-resistant or macrolide-resistant *S. pneumoniae* and in patients with penicillin allergies. Telithromycin is available only in oral formulation.³³

Adverse Reactions and Precautions

KEY POINT

Clinically significant drug interactions may occur with erythromycin, clarithromycin, telithromycin, and other drugs metabolized by the same hepatic enzymes, resulting in potentially life-threatening complications (i.e., arrhythmias and seizures with high serum concentrations of theophylline; bleeding with warfarin).

Clarithromycin, azithromycin, and telithromycin are generally better tolerated compared with erythromycin. The most common adverse reactions of these agents include gastrointestinal complaints, such as nausea, vomiting, abdominal cramps, and diarrhea. The use of intravenous erythromycin is associated with thrombophlebitis. Ventricular tachycardia and Q-T interval prolongation have been reported with the use of the macrolides, azithromycin, and telithromycin. Erythromycin, clarithromycin, and telithromycin are potent inhibitors of the hepatic drug metabolism system known as the *cytochrome P450 (CYP) system*. As a result, these agents can increase the systemic concentrations of drugs metabolized through the CYP system. For drugs with narrow therapeutic indices, such as theophylline, warfarin, and triazolam, this interaction can lead to potential life-threatening complications.³³

Fluoroquinolones

CLINICAL CONNECTION

Levofloxacin (Levaquin) is commonly used antibiotic in patients with pulmonary disorders (i.e., chronic obstructive pulmonary disease [COPD]).

Fluoroquinolones (Table 14.6) are a semisynthetic group of antimicrobials structurally related to nalidixic acid (quinolone), one of the byproducts of chloroquine synthesis. They are widely distributed into most body fluids and tissues (achieving high respiratory tract concentrations). Fluoroquinolones are eliminated primarily

through the kidneys and achieve high concentrations in urine. Agents from this class have variable activity against gram-negative bacteria, gram-positive bacteria, anaerobes, atypical bacteria, and mycobacteria. Ciprofloxacin, levofloxacin, and moxifloxacin are the most commonly used fluoroquinolones in the United States.^{35,36}

KEY POINT

Fluoroquinolones exert their antibacterial effect through inhibition of DNA synthesis and are considered bactericidal agents, showing concentration-dependent killing.

Mechanism of Action

Fluoroquinolones exert their antibacterial effect through inhibition of DNA synthesis. They inhibit topoisomerase II (DNA gyrase) and topoisomerase IV, which are necessary for bacterial replication. They are considered bactericidal agents and exhibit concentration-dependent killing.

Clinical Uses

Most fluoroquinolones have activity against the common respiratory pathogens, including *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. These agents have been shown to be effective in the treatment of upper and lower respiratory tract infections, genitourinary tract infections, and skin and skin structure infections. Fluoroquinolones do not penetrate cerebrospinal fluid to any significant extent. Ciprofloxacin has been shown to have the best in vitro activity of the fluoroquinolones against *P. aeruginosa* and other gram-negative aerobes. Ciprofloxacin and levofloxacin have been used for the treatment of nosocomial pneumonia.^{35,36}

Adverse Reactions and Precautions

Fluoroquinolones are well tolerated and are considered one of the safest antimicrobial classes. Gastrointestinal side effects, such as nausea, vomiting, and diarrhea, occur in less than 5% of patients treated with these agents. Prolongation of the Q-T interval (especially in female patients) has been reported. Seizures have been reported with ciprofloxacin in older patients and those with diminished renal function. Studies in immature laboratory animals have shown changes in weight-bearing joints after fluoroquinolone

TABLE 14.6 Classification and Clinical Uses of Fluoroquinolones^{35,36}

Generic Name	Brand Name	Route	Common Uses (Microorganisms)
Ciprofloxacin	Cipro	IV, PO	<i>Pseudomonas aeruginosa</i> , Enterobacteriaceae, <i>Neisseria gonorrhoeae</i> , <i>Mycoplasma pneumoniae</i> , <i>Legionella pneumophila</i>
Ofloxacin	Oflox	IV, PO	<i>P. aeruginosa</i> , Enterobacteriaceae, <i>N. gonorrhoeae</i> , <i>M. pneumoniae</i> , <i>Chlamydomphila pneumoniae</i> , <i>L. pneumophila</i>
Levofloxacin	Levaquin	IV, PO	<i>P. aeruginosa</i> , Enterobacteriaceae, <i>Streptococcus pyogenes</i> , MSSA, <i>Haemophilus influenzae</i> , <i>M. catarrhalis</i> , penicillin-resistant <i>Streptococcus pneumoniae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , <i>L. pneumophila</i>
Moxifloxacin	Avelox	PO	Enterobacteriaceae, <i>S. pyogenes</i> , MSSA, <i>H. influenzae</i> , <i>Moraxella catarrhalis</i> , penicillin-resistant <i>S. pneumoniae</i> , <i>M. pneumoniae</i> , <i>C. pneumoniae</i> , <i>L. pneumophila</i>

IV, Intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PO, oral.

exposure. Use of fluoroquinolones in children (18 years of age or younger) should be reserved for cases in which the benefits outweigh the risks. Drug interactions between fluoroquinolones and warfarin can increase the potential for bleeding, necessitating close monitoring of patients on warfarin. Dosage adjustment, except for moxifloxacin, is necessary in the presence of renal insufficiency. Concomitant use of antacids and iron supplements reduces the absorption of fluoroquinolones.³⁵

Other Antibiotics

Agents that belong to various classes of antimicrobials with different mechanisms of action and spectra of activity are described below. Individual agents are discussed when they represent the clinically used agents of their antimicrobial class.

Chloramphenicol

Chloramphenicol has a broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria. Chloramphenicol distributes well into various tissues, including the brain. Use of this antibiotic has declined significantly with the availability of less toxic agents.³⁷ Recently, there has been renewed interest in chloramphenicol because of its activity against multidrug-resistant gram-negative bacteria.³⁸

Mechanism of Action. Chloramphenicol inhibits protein synthesis by reversibly binding to the 50S ribosome subunit and essentially has a bacteriostatic effect. With prolonged exposure, chloramphenicol exhibits bactericidal activity against some organisms by inducing bacterial cell lysis.³⁷

Clinical Uses. Chloramphenicol is highly active against *Salmonella* and has been used for the treatment of gastroenteritis with sepsis and *Salmonella* meningitis. Chloramphenicol has excellent activity against rickettsial diseases, such as scrub typhus, murine typhus, and Rocky Mountain spotted fever. However, these diseases are usually treated with tetracyclines, with chloramphenicol reserved for pregnant patients. Anaerobic infections and mixed anaerobic-aerobic infections, such as peritonitis and aspiration pneumonia, can be treated with chloramphenicol. In addition, chloramphenicol can be used to treat bacteremias caused by *Enterococcus* species, including some isolates that are resistant to vancomycin.³⁷

Adverse Reactions and Precautions. Because of the possibility of irreversible bone marrow suppression that may lead to serious and fatal blood dyscrasias (aplastic anemia), chloramphenicol has little place in the antimicrobial armament at the present time. Aplastic anemia is a life-threatening complication reported in 1 of every 20,000 patients treated with chloramphenicol. Chloramphenicol should not be used in premature and newborn infants, who cannot adequately metabolize this drug. The decreased metabolism of chloramphenicol results in high serum concentrations that can lead to *gray baby syndrome* (vomiting, pallor, cyanosis, circulatory collapse), which has an attributable mortality of 60%. The prolonged use of chloramphenicol in children with CF has been associated with optic neuritis leading to blindness.³⁷

Colistin (Colistimethate)

CLINICAL CONNECTION

Colistimethate injectable solution is commonly aerosolized for treatment of *Pseudomonas aeruginosa* in cystic fibrosis. It does not come as an inhaled solution and is not approved by the US Food and Drug Administration (FDA) (see Chapter 17, Off Label Use).

Colistin, a member of the polymyxin family, was used in the early 1960s for serious gram-negative infections, including infections caused by *P. aeruginosa*. It was approved in 1968 by the FDA but was later abandoned for drugs with similar gram-negative efficacy and more favorable side effect profiles.²⁷ However, there has been a resurgence in the use of colistin because of the emergence of MDR gram-negative bacteria including *P. aeruginosa* and *Acinetobacter* species.

Mechanism of Action. Colistin is a surface-active, antipathic agent with a mechanism of action similar to that of a detergent. Because colistin has both hydrophilic and hydrophobic portions, it is relatively easy for the molecule to incorporate into bacterial cell membranes, causing disruption. Colistin exhibits bactericidal activity against most gram-negative bacteria.²⁷

Clinical Uses. Colistin has a broad range of activity against most gram-negative bacteria, including MDR *P. aeruginosa* and *Acinetobacter* species. Use of colistin is often reserved for severe systemic infections, including VAPs. *Proteus* and *Neisseria* species are generally resistant to colistin, along with most anaerobes and gram-positive bacteria. Colistin is administered in an inactive form (colistimethate) intravenously, intramuscularly, or by nebulization. After administration, inactive colistimethate is converted in vivo to the active form colistin.¹⁹ Nebulized colistin is used often in patients with CF who harbor MDR *P. aeruginosa* and *Acinetobacter*.²⁷

Adverse Reactions and Precautions. The most serious side effect associated with intravenously administered colistin is nephrotoxicity, which seems to be dose related and reversible. Nephrotoxicity has been reported to occur in 20% of patients given colistin. Neuromuscular blockage, seizures, and respiratory paralysis have also been reported and seem to be dose-dependent phenomena as well. Caution should be used when coadministering colistin with other agents capable of causing nephrotoxicity, neuromuscular blockage, or respiratory failure, such as aminoglycosides.²⁷

Daptomycin

KEY POINT

Daptomycin is a novel cyclic lipopeptide that has activity against a wide range of gram-positive bacteria, including multidrug-resistant (MDR) staphylococci and enterococci.

Daptomycin is a novel cyclic lipopeptide that has activity against a wide range of gram-positive bacteria, including MDR staphylococci and enterococci. However, daptomycin is inactive against gram-negative bacteria.^{39,40}

Mechanism of Action. The exact mechanism of daptomycin has not been completely elucidated; however, it is believed to occur by irreversible binding to the cytoplasmic membrane of bacterial cells and subsequent disruption of the membrane potential. This disruption apparently causes leakage of intracellular ions, leading to rapid cell death.³⁹

Clinical Uses. Daptomycin is currently approved for use in complicated skin and skin structure infections caused by susceptible gram-positive bacteria and *S. aureus* bacteremia. It has excellent activity against resistant staphylococci and enterococci, including vancomycin-resistant strains, although it is not approved for this use. In a phase III trial involving daptomycin for the treatment of CAP, daptomycin was inferior to the comparator agent (ceftriaxone), especially in patients with more serious infections. This poor response in pulmonary infections has been attributed to inactivation of daptomycin by pulmonary surfactants. Consequently,

daptomycin is not indicated for use in the treatment of pneumonia. It is available only as an intravenous infusion.^{39,40} With the increased incidence of MRSA in skin and soft tissue infections, daptomycin use has significantly increased because of its efficacy and convenience of a once-daily administration.

Adverse Reactions and Precautions. In earlier clinical studies involving daptomycin given every 8 to 12 hours, creatine phosphokinase (CPK) elevations and myalgias were noted that resulted in temporary suspension of drug development of this agent in the early 1990s. Once-daily administration of daptomycin has minimized these abnormalities noted in earlier studies. Clinical data have reported CPK elevations as a rare occurrence; however, the manufacturer recommends stopping hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (Lipitor, Zocor, Crestor, etc.) and other drugs associated with rhabdomyolysis during daptomycin therapy. In addition, daptomycin should be discontinued in patients with myalgias associated with CPK elevations or in asymptomatic patients with CPK elevations greater than 10 times the upper limit of normal.^{39,40}

Trimethoprim-Sulfamethoxazole

CLINICAL CONNECTION

Trimethoprim-Sulfamethoxazole (TMP-SMX) is used for the treatment and prophylaxis of *Pneumocystis pneumonia* (PCP) in patients with human immunodeficiency virus (HIV) infection.

Sulfamethoxazole belongs to the class of antibiotics known as *sulfonamides*. Trimethoprim is a pyrimidine found to potentiate the activity of sulfamethoxazole. The combination of trimethoprim and sulfamethoxazole (TMP-SMX; Bactrim) was introduced in 1968 and has since gained a place in the treatment of numerous infections. This combination is active against gram-positive bacteria (streptococci, MSSA, MRSA) and gram-negative bacteria (*H. influenzae*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*). In addition, it is active against *Pneumocystis jiroveci* (formerly named *Pneumocystis carinii*).⁴¹

Mechanism of Action. TMP-SMX exerts antibacterial effects by sequentially blocking bacterial dihydropteroate synthetase and dihydrofolate reductase. These enzymes are responsible for the production of folic acid. Without folic acid, bacteria are unable to synthesize nucleic acid and proteins necessary for growth. TMP-SMX acts synergistically and is considered bacteriostatic.⁴¹

Clinical Uses. TMP-SMX is used for the treatment and prophylaxis of *Pneumocystis pneumonia* (PCP) in patients infected with HIV. TMP-SMX is widely distributed in the body, achieving detectable levels in most tissues. High concentrations are achieved in urine, making it an ideal agent for the treatment of UTIs. In addition, TMP-SMX has been used for treatment of acute exacerbations of bronchitis, traveler's diarrhea caused by enterotoxigenic *E. coli*, otitis media, and shigellosis. In recent years, bacterial resistance to TMP-SMX has increased, creating controversy over the continued use of this combination as a first-line agent for treating UTIs. TMP-SMX also displays good activity against MRSA, including community-acquired strains, which gives practitioners an effective oral option for treatment.⁴¹

Adverse Reactions and Precautions. TMP-SMX is relatively well tolerated; nausea, vomiting, diarrhea, and hypersensitivity are the most common adverse effects. In addition, sulfamethoxazole has side effects that are common to all sulfonamides, including neutropenia, thrombocytopenia, hemolytic anemia, jaundice, hepatic necrosis, and drug-induced lupus. TMP-SMX should be

avoided in all patients with “sulfa” allergies or hypersensitivities. Patients who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) should not receive TMP-SMX because this combination can increase the risk of hemolytic anemia. TMP-SMX has a significant drug interaction with warfarin, which can increase the risk of bleeding. The daily dosage of TMP-SMX should be reduced in the presence of renal insufficiency because both agents are eliminated through the kidneys. Patients should be advised to take TMP-SMZ with 8 ounces of water to prevent acute interstitial nephritis.⁴¹

Clindamycin

Clindamycin, a member of the lincosamide class of antibiotics, has activity against gram-positive and anaerobic bacteria. In addition, this agent is active against *Toxoplasma gondii* and *P. jiroveci*.^{37,42}

Mechanism of Action. Similar to chloramphenicol, clindamycin binds to the bacterial 50S ribosomal subunit to inhibit protein synthesis, resulting in a bacteriostatic effect. This suppression of protein synthesis has been shown to reduce toxin production in certain strains of *S. aureus* (toxic shock syndrome) and *S. pyogenes* (necrotizing fasciitis).^{37,42}

Clinical Uses. Clindamycin distributes well in body tissues but has minimal penetration into cerebrospinal fluid even in the presence of meningitis. Clindamycin is used as an adjunct to agents with gram-negative activity for intraabdominal, pelvic, and diabetic foot infections, all of which tend to be polymicrobial. Anaerobic infections of the respiratory tract, such as necrotizing pneumonia, lung abscess, empyema, and aspiration pneumonia, are often treated with clindamycin. AIDS-related illnesses, such as *Toxoplasma encephalitis* and PCP, can also be treated with clindamycin. Clindamycin also has significant activity against MRSA, including community-acquired strains.^{37,42}

Adverse Reactions and Precautions. Nausea, vomiting, and diarrhea are the most common side effects associated with clindamycin. Diarrhea may be a consequence of *Clostridioides difficile*. Discontinuing the offending antibiotic and initiating oral vancomycin or metronidazole therapy treats this mild to life-threatening diarrhea. Prolongation of the neuromuscular blocking effects of pancuronium with the concomitant use of clindamycin has also been reported.^{37,42}

Metronidazole

Metronidazole is a nitroimidazole that was used initially for its antiprotozoal effects against some pathogens, such as *Trichomonas vaginalis*, *Giardia lamblia*, and *Entamoeba histolytica*. Its anaerobic properties were discovered after an observation that acute ulcerative gingivitis improved in patients being treated for trichomonal vaginitis.³⁷

Mechanism of Action. The exact mechanism of action of metronidazole is unknown, although it is thought to have different effects in protozoa versus anaerobic bacteria. It is postulated that the microorganisms convert metronidazole into its reduced form. This reduced form causes a loss of the helical structure of DNA and results in DNA strand breaks. Metronidazole is bactericidal against most anaerobic pathogens, such as *B. fragilis*.³⁷

Clinical Uses. Anaerobic infections have been implicated in abscesses within the brain, lung, and intraabdominal cavity. Metronidazole is often added as an adjunct, especially when surgical drainage of the abscess is impossible. In contrast to clindamycin, metronidazole penetrates well into the central nervous system and is useful for the treatment of brain abscesses. A key anaerobic pathogen, *B. fragilis* is part of the normal enteric flora and can contribute to sepsis in the event of gastrointestinal disease, surgery, or

penetrating trauma. Metronidazole is often added to treat polymicrobial infections, especially when *B. fragilis* is suspected. Bacterial vaginosis caused by *Gardnerella*, *Trichomonas*, and *Bacteroides* species is also treated with metronidazole. In addition, diarrhea caused by *C. difficile* can be treated with metronidazole.³⁷

Adverse Reactions and Precautions. An unpleasant metallic taste, nausea, and vomiting are common complaints associated with the use of metronidazole. The prolonged use of metronidazole, especially with high doses, can lead to peripheral neuropathy. In some rare situations, seizures, encephalopathy, and cerebellar dysfunction have also been noted. Metronidazole can interact with warfarin to potentiate its hypoprothrombinemic effect and lead to significant bleeding. In addition, patients should avoid the use of alcohol while taking metronidazole (inhibits alcohol dehydrogenase) because the concomitant use can result in a disulfiram-like reaction.³⁷

Glycopeptides

Vancomycin. Vancomycin is a glycopeptide antibiotic with activity against gram-positive bacteria. It is not active against gram-negative bacteria. Its use in recent years has increased as a result of the emergence of MRSA.^{40,43}

CLINICAL CONNECTION

Vancomycin is a glycopeptide antibiotic with activity against gram-positive bacteria (i.e., methicillin-resistant *Staphylococcus aureus* [MRSA]). It is not active against gram-negative bacteria.

Mechanism of Action. Vancomycin inhibits transglycosylation of peptidoglycan by binding to the precursor d-alanine-d-alanine portion. This process prevents the formation of a rigid cell wall structure and results in bacterial cell lysis. Vancomycin is considered bactericidal against gram-positive organisms with the exception of enterococci (bacteriostatic).^{40,43}

Clinical Uses. Vancomycin is used for infections caused by MRSA, such as bacteremias, endocarditis, pneumonia, peritonitis, and skin and soft tissue infections. Vancomycin also serves as the alternative agent to penicillin for the treatment of viridans streptococcal endocarditis. Vancomycin does not cross the blood–brain barrier efficiently, even in the presence of acute meningeal inflammation. However, pneumococcal meningitis resistant to penicillin can still be treated with these low concentrations of vancomycin. An oral formulation of vancomycin can be used to treat *C. difficile* diarrhea that is refractory to metronidazole.^{40,43}

Adverse Reactions and Precautions. A common reaction known as *red man syndrome*, or *red neck syndrome*, has been associated with the rapid infusion of vancomycin (related to histamine release). Increasing the time of infusion can prevent this syndrome of skin itch, flushing, angioedema, and hypotension. Ototoxicity and nephrotoxicity have been noted to occur more frequently in patients who receive vancomycin concomitantly with aminoglycosides. Vancomycin is renally excreted and requires dosage adjustment in patients with renal impairment.^{40,43}

Telavancin, Delbavancin, and Oritavancin. Telavancin (Vibativ), delbavancin (Dalvance), and oritavancin (Orbactiv) are lipoglycopeptides structurally related to vancomycin. Similar to vancomycin, these drugs display no activity against gram-negative bacteria; however, they have excellent activity against most gram-positive isolates, including those with resistance to vancomycin.^{40,43,44}

Mechanism of Action. Similar to vancomycin, telavancin, delbavancin, and oritavancin inhibit transglycosylation of peptidoglycan by binding to the precursor d-alanine-d-alanine portion

of the gram-positive cell wall. The lipophilic side chain on the lipoglycopeptides also appears to anchor these agents into the cell wall, which may contribute to their enhanced potency over vancomycin.^{40,44}

Clinical Uses. Telavancin, delbavancin, and oritavancin are used for infections caused by *S. aureus*, enterococci, and streptococci. Unlike vancomycin, the lipoglycopeptides have activity against those isolates with reduced susceptibility to vancomycin, including vancomycin-resistant *Enterococcus faecium* (VREF), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA). Telavancin is approved for use in complicated skin and skin structure infections, as well as in HAP and VAP caused by *S. aureus*. Like vancomycin, it can be used as an alternative agent for gram-positive infections in individuals with β -lactam allergies. Delbavancin and oritavancin are also approved for complicated skin and skin structure infections, with the added benefits of prolonged half-lives (once weekly, 2-dose, or single dose regimens).^{40,44–46}

Adverse Reactions and Precautions. Lipoglycopeptides are generally well tolerated, with only mild side effects reported, to date. Dysgeusia (taste disturbances), nausea, and headache were the most commonly reported adverse reactions during clinical trials. Dizziness and infusion site reactions were also observed, but at a similar rate to those receiving vancomycin. In addition, delbavancin and oritavancin both caused notable increases in transaminases during clinical trials.^{40,44–46}

Quinupristin and Dalfopristin

Quinupristin and dalfopristin are streptogramins that act synergistically when used together (as in the product Synercid). These agents are active against gram-positive bacteria and are used primarily to treat infections caused by VREF.⁴⁰

Mechanism of Action. Dalfopristin blocks peptide bond formation and distorts the ribosome to enhance the binding of quinupristin. The ribosome-bound quinupristin inhibits the binding of aminoacyl-transfer RNA to inhibit protein synthesis. The combination is bactericidal against MRSA but is bacteriostatic against VREF.⁴⁰

Clinical Uses. Quinupristin-dalfopristin is used primarily for life-threatening VREF infections, but it is also indicated for skin and soft tissue infections and pneumonias caused by susceptible gram-positive pathogens. Quinupristin-dalfopristin is inactive against most gram-negative bacteria and anaerobes. However, quinupristin-dalfopristin has good in vitro activity against *M. pneumoniae* and *L. pneumophila*.⁴⁰

Adverse Reactions and Precautions. Quinupristin-dalfopristin is available only as a parenteral formulation and must be administered through a central line (catheter inserted and threaded to the superior or inferior vena cava) because peripheral administration is associated with a high incidence of thrombophlebitis. Arthralgias and myalgias of varying severity have also been reported with the use of these agents in up to 40% of patients. Similar to erythromycin, quinupristin-dalfopristin is an inhibitor of the CYP system. Drugs (metabolized through the CYP system) with a narrow therapeutic index should be used cautiously in patients receiving quinupristin-dalfopristin.⁴⁰

Oxazolidinones

Linezolid. The antibiotic linezolid belongs to a novel class of antibiotics known as *oxazolidinones*. Linezolid, similar to quinupristin-dalfopristin, is active against gram-positive bacteria and is approved for the treatment of severe life-threatening VREF infections. In contrast to vancomycin and quinupristin-dalfopristin,

linezolid is available as an oral formulation that is completely absorbed from the gastrointestinal tract.⁴⁰ Tedizolid is a new oxazolidinone agent with similar activity to linezolid but with activity against some linezolid-resistant strains of gram-positive bacteria. Currently, it has only been used in skin and skin structure infections.

Mechanism of Action. Linezolid prevents RNA translation by binding to the 23S ribosomal RNA of the 50S subunit to prevent the formation of a functional 70S initiation complex. Use of this novel antimicrobial target for the inhibition of protein synthesis has not been previously exploited.⁴⁰

Clinical Uses. Linezolid is indicated for the treatment of VRE infections, including cases with concurrent bacteremia. Nosocomial pneumonias and complicated skin and skin structure infections caused by *S. aureus*, including MRSA, may be treated with linezolid. Linezolid has activity against some mycobacterial species; however, it lacks significant activity against gram-negative bacteria.⁴⁰

Adverse Reactions and Precautions. The most common adverse events reported with linezolid include diarrhea, nausea, and headaches. Thrombocytopenia has been reported with the use of linezolid but is associated with prolonged use of the antibiotic (2 weeks or greater). Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and has the potential to interact with adrenergic agents (e.g., dopamine, norepinephrine) and serotonergic agents (e.g., selective serotonin reuptake inhibitors).⁴⁰

Antimycobacterials

Tuberculosis has received heightened attention largely because of the increase in cases attributed to the HIV epidemic. Each year, millions of individuals are exposed to tuberculosis, many through casual contact. More than one third of the world's population has contracted tuberculosis. The US Centers for Disease Control and Prevention (CDC) makes annual recommendations for the prevention and treatment of tuberculosis infection. Nosocomial transmission can be prevented by placing patients with suspected

or confirmed tuberculosis in respiratory isolation (negative-pressure room) until they are (1) determined not to have tuberculosis, (2) discharged from the hospital, or (3) confirmed to be noninfectious. Other measures, such as fitted respiratory masks (used by health care personnel), can prevent transmission of *M. tuberculosis* by aerosolization to caregivers.

Treatment consists of multiple antibiotic regimens for 6 to 12 months in duration. Single-agent regimens should never be used for treatment because the likelihood of developing resistance is high. Treatment failures often result from poor patient compliance and from resistance to antibiotics. Drugs used in the treatment of tuberculosis can be categorized as either first-line or second-line agents, depending on their efficacy and side effect profiles. Initial therapy generally involves a combination of isoniazid (INH), pyrazinamide, rifampin, and ethambutol. In cases of multidrug resistant tuberculosis, use of additional antimicrobials and newer agents, such as bedaquiline and pretomanid, is often required with selection based on isolate susceptibility and MIC testing. Table 14.7 provides a summary of clinically used antimycobacterial agents, doses, routes of administration, and side effects. Addition or subtraction of agents from this regimen is usually based on culture and sensitivity data, along with patient response to treatment. Guidelines for the treatment of active pulmonary tuberculosis are provided in Table 14.8.^{47,48}

CLINICAL CONNECTION

The most commonly used antimycobacterials in the treatment of tuberculosis include isoniazid (INH), rifampin, rifabutin, pyrazinamide, ethambutol, and streptomycin.

Isoniazid

INH is well absorbed orally and is distributed throughout the body, especially in cerebrospinal fluid. INH is metabolized by the liver, and its metabolite is eliminated by the kidneys.⁴⁹

TABLE 14.7 Dose, Route, and Side Effect Profile of Commonly Used Antimycobacterials^{47–49}

Antimycobacterial	Adult Dosage	Route	Side Effects
Isoniazid	5 mg/kg/day; maximum 300 mg/day	PO, IM	Hepatotoxicity (symptoms include nausea, loss of appetite, abdominal pain), peripheral neuritis, rash, fever, anemia
Rifampin	10 mg/kg/day; maximum 600 mg/day	PO, IV	Hepatotoxicity, flu-like symptoms, discolorations of body secretions to an orange color
Rifabutin	300 mg/day	PO	
Rifapentine	600 mg once or twice per week	PO	
Pyrazinamide	15–30 mg/kg/day; maximum 2000 mg/day	PO	Hepatotoxicity, arthralgia, hyperuricemia
Ethambutol	15–25 mg/kg/day; maximum 2500 mg/day	PO	Optic neuritis (greater incidence in patients receiving >15 mg/kg/day)
Streptomycin	15 mg/kg/day; maximum 1000 mg/day	IM	Ototoxicity (high-frequency hearing loss, vertigo), nephrotoxicity
Bedaquiline	400 mg/day for 2 weeks followed by 200 mg three times per week	PO	Arthralgia, headache, nausea
Pretomanid	200 mg/day	PO	Hepatotoxicity, peripheral nerve disease, anemia

IM, Intramuscular; IV, intravenous; PO, oral.

TABLE 14.8**Guidelines for Treatment of Active Drug-Susceptible Pulmonary Tuberculosis⁴⁸**

Regimen	TREATMENT REGIMEN		Considerations
	Intensive Phase INH, RIF, PZA, EMB	Continuation Phase INH, RIF	
1	7 d/wk or 5 d/wk for 8 weeks	7 d/wk or 5 d/wk for 18 weeks	Preferred regimen
2	7 d/wk or 5 d/wk for 8 weeks	3 d/wk for 18 weeks	Preferred when DOT is unachievable during continuation phase
3	3 d/wk for 8 weeks	3 d/wk for 18 weeks	Use cautiously in patients with cavitary disease and/or HIV
4	7 d/wk for 14 doses, then 2 d/wk for 12 doses	2 d/wk for 18 weeks	Do not use in cavitary disease, HIV-infected, and/or smear positive patients

DOT, directly observed therapy; *EMB*, ethambutol; *HIV*, human immunodeficiency virus; *INH*, isoniazid; *PZA*, pyrazinamide; *RIF*, rifampin; d/wk, days per week.

Mechanism of Action

INH inhibits cell wall synthesis by inhibiting synthesis of mycolic acid, a primary component of the mycobacterial cell wall. This agent is bactericidal against replicating tuberculosis bacilli and bacteriostatic against nonreplicating organisms.⁴⁹

Adverse Reactions and Precautions

An elevation in liver enzymes has been reported in patients receiving INH and is reversible with discontinuation of the drug. Rare cases of serious hepatitis and death also have been reported. Hepatotoxicity usually occurs between the fourth and eighth weeks of treatment but may occur at any time. Tests used to measure hepatocellular injury should be performed and include monitoring liver transaminases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In addition, patients should be monitored for the development of symptoms of hepatitis, such as nausea, loss of appetite, and abdominal pain. Neurotoxicity has also been reported and occurs more frequently in patients receiving higher-dose therapy. Supplementation with pyridoxine (vitamin B₆) has been shown to reduce the frequency of this adverse reaction. Rare miscellaneous reactions, such as rash, anemia, and fever, have also been reported.⁴⁹

Rifampin, Rifabutin, and Rifapentine

Rifampin, rifabutin, and rifapentine are semisynthetic antibiotics referred to as *rifamycins*. Rifampin and rifabutin have similar structures and spectra of activity. They are well absorbed orally, with good penetration into most tissues. These agents do not penetrate the central nervous system well in the absence of inflammation. Rifampin is extensively metabolized through the liver and is an inducer of the CYP system. Rifabutin and rifapentine are also metabolized hepatically; however, they are considered weaker enzyme inducers than rifampin. CYP induction is known to decrease plasma concentrations of drugs hepatically metabolized; therefore, dosage adjustments of agents metabolized by this system are necessary.⁵⁰

Mechanism of Action

Rifamycins inhibit bacterial DNA-dependent RNA polymerase. They are bactericidal against actively dividing bacteria.

Adverse Reactions and Precautions

Hepatotoxicity is the major adverse reaction associated with rifamycins. Elevations of liver transaminases are commonly reported

and are usually reversible on discontinuation of the drug. Patients with preexisting liver damage are more prone to rifamycin-induced hepatotoxicity. Rifamycins are known to change the color of body fluids to a deep orange hue. Patients should be warned that urine, feces, tears, saliva, sputum, and semen might turn an orange color. Uveitis (inflammation of the iris), which manifests as blurry vision, has also been reported. Rarely, flu-like symptoms, such as fever, chills, nausea, and vomiting, have been reported during rifamycin therapy.⁵⁰

Pyrazinamide

Pyrazinamide is a nicotinic acid derivative that is well distributed into most tissues, including cerebrospinal fluid. Pyrazinamide is hepatically metabolized and excreted by the kidneys.⁴⁹

Mechanism of Action

The precise mechanism of action is unknown. Mycobacteria convert pyrazinamide to pyrazinoic acid. It is speculated that pyrazinoic acid accumulates in macrophages to decrease the intracellular pH and increase the antimycobacterial activity of macrophages in combination with pyrazinamide. Pyrazinamide is bactericidal against mycobacteria when tested in an acidic environment.⁴⁹

Adverse Reactions and Precautions

Nausea and vomiting are the most common side effects with pyrazinamide treatment. Hepatotoxicity has also been reported in patients receiving pyrazinamide; therefore, liver transaminases should be monitored frequently. Patients with preexisting liver abnormalities should be monitored closely. Pyrazinamide is not known to induce or inhibit the CYP system to any significant extent.⁴⁹

Ethambutol

Ethambutol is a synthetic, orally administered agent that distributes extensively throughout the body, including cerebrospinal fluid. Most of it is eliminated unchanged in urine.⁴⁹

Mechanism of Action

Ethambutol decreases the synthesis of cell wall polysaccharides, such as arabinogalactan, to inhibit mycobacterial cell growth. It is a bacteriostatic agent.

Adverse Reactions and Precautions

Optic neuropathy is the major toxicity associated with ethambutol. Patients usually complain of blurred vision in conjunction with altered color (red–green) perception. Optic neuritis is usually seen with the use of high doses of ethambutol and is slowly reversible on discontinuation of the drug. Baseline optometric evaluation, followed by periodic examinations, is advisable to help monitor for visual changes during treatment. The dosage of ethambutol should be adjusted in patients with renal insufficiency.⁴⁹

Streptomycin

Streptomycin is an aminoglycoside antibiotic that has been in use since the 1940s for the treatment of tuberculosis. It is available for use intravenously and intramuscularly and is indicated as an add-on agent in patients with documented or suspected drug-resistant tuberculosis.^{26–29,49}

Mechanism of Action

Streptomycin has a mechanism of action similar to other aminoglycosides.

Adverse Reactions and Precautions

Streptomycin, similar to other aminoglycosides, is associated with nephrotoxicity and ototoxicity. It is eliminated unchanged in urine, and dosage adjustment is required in patients with renal insufficiency.^{26–29}

Antifungals

KEY POINT

Use of antifungals, such as polyenes, azoles, and echinocandins, is increasing with the growing number of immunocompromised patients.

The incidence of fungal infections has increased dramatically. *Candida* species are now the fourth most commonly isolated bloodstream pathogens. Candidemia has a mortality rate of 40%. The number of patients immunocompromised as a result of AIDS, cancer chemotherapy, and organ transplantation has been increasing. These patient populations have diminished cell-mediated immunity and are predisposed to numerous fungal pathogens that vary in incidence geographically. The treatment of choice for most fungal infections has been the polyene amphotericin B. The high incidence of nephrotoxicity associated with this agent served as the impetus for the development of the azoles. Ketoconazole was the first agent of this class, but it has largely been replaced by the triazoles fluconazole and itraconazole. Newer triazoles with improved activity against molds are being developed. In addition, a new class of antifungals known as *echinocandins* is now available. Systemically used antifungals, including route and clinical uses, are summarized in [Table 14.9](#).

Polyenes

Polyenes include amphotericin B and nystatin. Amphotericin B has been available for more than 50 years and remains the drug of choice for most systemic fungal infections. More recently, amphotericin B has been largely replaced by the lipid-based formulation. These lipid-based products alter the distribution of amphotericin B, resulting in a higher uptake of the agent into

the reticuloendothelial system (liver, spleen, lymphatics) relative to the kidneys. The net effect of this shift in distribution has been shown to reduce the incidence of nephrotoxicity.⁵¹

Mechanism of Action

Polyenes bind to ergosterol (a type of cholesterol) in the fungal cell membrane, creating pores that increase cell membrane permeability. Intracellular potassium and other components escape through the pores, resulting in cell death (fungicidal).

Clinical Uses

The fungicidal activity of amphotericin B has made it the first-line agent against several pathogens causing pulmonary infections, including aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, and cryptococcosis. These infections are associated with a high mortality, especially in patients with neutropenia. Consequently, preventive measures, such as amphotericin B prophylaxis and high-dose treatment (through the use of lipid-based formulations), have been sought. However, the optimal dose and treatment duration have been difficult to define because the successful outcome of a systemic fungal infection depends largely on recovery of the host immune system.⁵¹

Adverse Reactions and Precautions

Parenteral administration of amphotericin B is associated with two major types of toxicity. The first is infusion related and includes flushing, fever, and chills. Pretreating patients who exhibit these symptoms with antipyretics and antihistamines may minimize these effects. The second major toxicity is renal impairment, thought to be a result of diminished renal perfusion. Hydrating the patient with normal saline boluses before and after amphotericin B infusion has been attempted to prevent this toxicity. The liposomal products, such as amphotericin B lipid complex and liposomal amphotericin B, have been shown to be less nephrotoxic compared with the traditional product and allow for administration of higher doses of amphotericin B.⁵¹

Azoles

Systemically used azoles include ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole. Ketoconazole was the first oral agent available to treat systemic fungal infections. This agent is poorly absorbed from the gastrointestinal tract (when an acidic environment is not present) and has potential for substantial toxicity. As a result, ketoconazole has largely been replaced by the newer triazoles fluconazole, itraconazole, voriconazole, and isavuconazole. Fluconazole is available in oral and intravenous formulations, is widely distributed into the tissues, and is relatively nontoxic. Compared with ketoconazole, it has a narrow spectrum of activity. Itraconazole has an enhanced spectrum of activity compared with fluconazole but slightly less than that of voriconazole. Voriconazole is also available in oral and intravenous forms. Posaconazole was approved more recently for prophylaxis of invasive aspergillosis and disseminated candidiasis in severely immunocompromised hosts and for the treatment of refractory oropharyngeal candidiasis. Use of posaconazole is intended for patients failing or refractory to other therapies and has been documented to be active against *Zygomycetes* (*Rhizopus* species, *Absidia* species, and *Mucor* species). Isavuconazole, supplied as the prodrug isavuconazonium sulfate, was recently approved for invasive aspergillosis and mucormycosis. Unlike

TABLE 14.9 Classification of Systemically Used Antifungals^{51–52}

Antifungal Class and Generic Name	Brand Name	Route	Common Uses (Microorganism)
Polyenes			
Amphotericin B	Fungizone	IV, PO*	<i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Blastomyces dermatitidis</i> , <i>Coccidioides immitis</i>
Amphotericin B colloidal dispersion	Amphotec	IV	<i>Candida</i> spp., <i>Aspergillus</i> spp., mucormycosis, <i>C. neoformans</i>
Amphotericin B lipid complex	Abelcet	IV	<i>Candida</i> spp., <i>Aspergillus</i> spp., mucormycosis, <i>C. neoformans</i>
Liposomal amphotericin B	AmBisome	IV	<i>Candida</i> spp., <i>Aspergillus</i> spp., mucormycosis, <i>C. neoformans</i> , leishmaniasis
Azoles			
Ketoconazole	Nizoral	PO, TOP	<i>Candida</i> spp., [†] <i>C. neoformans</i> , <i>H. capsulatum</i> , <i>B. dermatitidis</i>
Fluconazole	Diflucan	IV, PO	<i>Candida</i> spp., [†] <i>C. neoformans</i>
Isavuconazonium sulfate (isavuconazole prodrug)	Cresemba	IV, PO	<i>Aspergillus</i> spp., <i>Mucormycetes</i> spp.
Itraconazole	Sporanox	PO, TOP	<i>Candida</i> spp., [†] <i>Aspergillus</i> spp., <i>C. neoformans</i> , <i>H. capsulatum</i> , <i>B. dermatitidis</i> , <i>C. immitis</i> , <i>Sporothrix schenckii</i>
Voriconazole	Vfend	IV, PO	<i>Candida</i> spp., [†] <i>Aspergillus</i> spp., <i>C. neoformans</i> , <i>C. immitis</i> , <i>H. capsulatum</i> , <i>B. dermatitidis</i> , <i>Fusarium</i> spp., <i>Scedosporium</i> spp.
Posaconazole	Noxafil	PO	<i>Candida</i> spp., [†] <i>Aspergillus</i> spp., <i>C. neoformans</i> , <i>C. immitis</i> , <i>H. capsulatum</i> , <i>B. dermatitidis</i> , <i>Fusarium</i> spp., <i>Scedosporium</i> spp.
Echinocandins			
Caspofungin	Cancidas	IV	<i>Aspergillus</i> spp., <i>Candida</i> spp.
Micafungin	Mycamine	IV	<i>Aspergillus</i> spp., <i>Candida</i> spp.
Anidulafungin	Eraxis	IV	<i>Aspergillus</i> spp., <i>Candida</i> spp.
Other Antifungals			
Flucytosine	Ancobon	PO	<i>Aspergillus</i> spp., <i>Candida</i> spp., <i>C. neoformans</i>

IV, Intravenous; PO, oral; TOP, topical.

*The oral form of amphotericin B is not absorbed through the gastrointestinal tract.

[†]*Candida krusei* is intrinsically resistant to all azoles.

voriconazole and posaconazole, isavuconazonium sulfate is highly water soluble and the intravenous formulation does not require a cyclodextrin vehicle, reducing nephrotoxicity. In addition, the isavuconazonium sulfate oral formulation possesses excellent bioavailability and therefore more predictable pharmacokinetics.^{51,52}

Mechanism of Action

Fungal cell growth is impaired because of the reduced production of ergosterol. Azoles prevent the conversion of lanosterol to ergosterol by inhibiting the fungal CYP system and therefore produce a fungistatic effect.

Clinical Uses

Ketoconazole has largely been replaced by the more potent and better tolerated triazoles. The primary indication for fluconazole is for candidiasis (patients without neutropenia) and as suppressive therapy for patients with cryptococcal meningitis, but it may also be used to treat coccidioidomycosis. Itraconazole is considered

the drug of choice for the treatment of cutaneous and lymphatic sporotrichosis. Itraconazole is also used as prophylaxis and suppressive therapy for pulmonary aspergillosis, histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis, paracoccidioidomycosis, and candidiasis. Voriconazole is indicated for invasive aspergillosis and has been approved for the management of candidemia and infections caused by rare pathogens, such as *Fusarium* and *Scedosporium apiospermum*. Isavuconazonium sulfate is also indicated for invasive aspergillosis and invasive mucormycosis, with efficacy similar to amphotericin B and posaconazole. Candidiasis caused by *Candida krusei* (which lacks the CYP system) may be intrinsically resistant to this class of agents, although in vitro activity has been documented with voriconazole and posaconazole.^{51,52}

Adverse Reactions and Precautions

Fluconazole is well tolerated and has minimal side effects. Common adverse effects with ketoconazole, itraconazole,

isavuconazonium sulfate, and voriconazole are anorexia, nausea, and vomiting. In addition, transaminase and bilirubin elevations have been reported. Impotence, decreased libido, and gynecomastia are also known to occur with ketoconazole and are attributed to its inhibition of sex steroid synthesis, and consequently it is used clinically for certain endocrine disorders. Voriconazole can cause visual disturbances, such as photopsia and chromatopsia, which can occur in 30% of patients. Ketoconazole, itraconazole, isavuconazole, and voriconazole are metabolized in the liver and are potent inhibitors of the CYP 3A4 system, so each has a significant potential for drug interactions. Conversely, fluconazole does not undergo significant hepatic metabolism and has the lowest drug interaction potential of the triazoles. Fluconazole is, however, eliminated unchanged in the urine and so dosage adjustment is required in patients with impaired renal function. Renal function is also important when administering the intravenous formulations of itraconazole and voriconazole. These drugs should be avoided in patients with creatinine clearance values less than 30 mL/min to prevent the accumulation of cyclodextrin, an intravenous solubilizing agent. Cyclodextrin is also used to formulate oral itraconazole solution and has been cited as the cause of the high incidence of adverse gastrointestinal intolerance relative to itraconazole capsules, which do not contain this agent.^{51,52}

Echinocandins

Caspofungin was the first echinocandin to receive FDA approval in early 2001. Micafungin and anidulafungin received FDA approval in 2004 and 2006, respectively. These agents have similar pharmacokinetic and pharmacodynamic properties. They have poor gastrointestinal absorption, and all require parenteral administration.⁵¹

Mechanism of Action

Echinocandins inhibit fungal cell wall synthesis by inhibiting (1,3)- β -D-glucan synthase.⁵¹

These agents may be either fungicidal or fungistatic against fungi, depending on the isolate.

Clinical Uses

All echinocandins have shown in vitro and in vivo (animal studies) activity against *Candida* and *Aspergillus* species. Caspofungin is currently indicated for the treatment of febrile neutropenia, candidemia, esophageal candidiasis, and aspergillosis in patients refractory or intolerant to amphotericin B, lipid-based amphotericin B, and itraconazole. Micafungin is indicated only for esophageal candidiasis treatment and prophylaxis after hematopoietic stem cell transplants. Anidulafungin, the most recently approved agent, is indicated for the treatment of candidemia, nonneutropenic candidiasis, and esophageal candidiasis. All echinocandins are considered ineffective against *Cryptococcus* species because these organisms lack (1,3)- β -D-glucan in their cell walls.⁵¹

Adverse Reactions and Precautions

Echinocandins seem to be well tolerated, although most of the safety data are for caspofungin and micafungin. In most studies, common adverse reactions were infusion related and included fever, rash, flushing, and thrombophlebitis. Infusion-related reactions were approximately 10% for caspofungin and slightly less for micafungin. Anidulafungin has produced infusion-related reactions in 15% of patients. Nausea and vomiting were also frequently reported for all three agents. Elevations in liver

transaminase (AST and ALT) levels and hyperbilirubinemia were noted with echinocandins, but these were mild and reversible on drug discontinuation. Echinocandins are not metabolized through the CYP system, reducing the potential for drug interactions. All echinocandins can increase the area under the curve (AUC) of cyclosporine when coadministered, with caspofungin creating the most significant changes in the AUC. The mechanism of this interaction is unknown. Concurrent use of cyclosporine and echinocandins may warrant careful monitoring.⁵¹

Flucytosine

Flucytosine acts as an antimetabolite and is used primarily as adjunctive therapy for susceptible fungal pathogens. It is active against *Candida*, *Cryptococcus*, and *Aspergillus*.⁵¹

Mechanism of Action

Flucytosine is converted to fluorouracil and competes with uracil during the formation of fungal RNA. Inhibition of RNA formation decreases protein synthesis and prevents cell growth (fungistatic).

Clinical Use

Resistance to flucytosine develops rapidly when it is used as a single agent for systemic fungal infections. As a result, flucytosine has been used in combination with amphotericin B for the treatment of cryptococcal meningitis and aspergillosis.⁵¹

Adverse Reactions and Precautions

The most common adverse event associated with flucytosine is bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia. This toxicity usually results when serum concentrations exceed 100 mcg/mL. Dosage reduction in patients with renal impairment is imperative to prevent this serious complication.

Antiviral Agents

KEY POINT

Antivirals (excluding antiretrovirals) mimic nucleosides and inhibit DNA synthesis.

Several agents are available for treating viral infections (Table 14.10). All of these agents act by inhibiting steps involved in viral replication; none of the agents inhibit nonreplicating viruses. Antivirals (excluding antiretrovirals) mimic nucleosides and inhibit DNA synthesis.^{53,54} Agents used to treat HIV are not discussed here.

Acyclovir and Valacyclovir

Acyclovir is available in intravenous, oral, and topical formulations. Oral acyclovir is not readily absorbed and requires a frequent daily regimen. Valacyclovir, a prodrug of acyclovir, was developed to improve gastrointestinal absorption of acyclovir. Valacyclovir is available only in oral formulation.⁵³

Mechanism of Action

Acyclovir is a nucleoside analog that is phosphorylated and inserted into the replicating viral DNA. Once inserted in the growing chain, viral replication is terminated. Valacyclovir is

TABLE 14.10 Classification of Antivirals^{53–55}

Generic Name	Brand Name	Route	Common Uses (Microorganism)
Acyclovir	Zovirax	IV, PO, TOP	HSV-1, HSV-2, HZV, VZV
Valacyclovir	Valtrex	PO	HSV-1, HSV-2, HZV, VZV
Famciclovir	Famvir	PO	HSV-1, HSV-2, HZV, VZV
Ganciclovir	Cytovene	IV, PO	CMV
Valganciclovir	Valcyte	PO	CMV
Cidofovir	Vistide	IV	CMV
Foscarnet	Foscavir	IV	HSV-1, HSV-2, VZV, CMV that are suspected to be resistant to acyclovir and ganciclovir
Amantadine	Symadine	PO	Influenza A
Rimantadine	Flumadine	PO	Influenza A
Oseltamivir	Tamiflu	PO	Influenza A and B
Peramivir	Rapivab	IV	Influenza A and B
Zanamivir	Relenza	IH	Influenza A and B
Baloxavir marboxil	Xofluza	PO	Influenza A and B

CMV, Cytomegalovirus; HSV-1, -2, herpes simplex virus types 1 and 2; HZV, herpes zoster virus; IH, inhaled; IV, intravenous; PO, oral; TOP, topical; VZV, varicella-zoster virus.

converted to the active drug acyclovir by enzymatic hydrolysis in the liver and the intestines.

Clinical Uses

Acyclovir and valacyclovir are effective against members of the herpesvirus family. They are most effective against herpes simplex virus (HSV)-1 and HSV-2. They also have activity against Epstein-Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV). Acyclovir and valacyclovir are clinically used for the treatment of genital infections caused by HSV and VZV.⁵⁴

Adverse Reactions and Precautions

Acyclovir is eliminated unchanged in the urine; therefore dosage adjustment is required for acyclovir and valacyclovir in patients with renal impairment. Cases of nephropathy secondary to acyclovir have been reported in individuals with renal impairment. This adverse event occurs primarily in patients taking high doses of acyclovir. Keeping patients well hydrated can prevent nephropathy. The oral formulations are generally well tolerated.⁵⁴

Penciclovir and Famciclovir

Penciclovir and famciclovir are similar in structure and activity to acyclovir. Famciclovir, the prodrug of penciclovir, is converted to its active form (penciclovir) in the gastrointestinal tract. Famciclovir is available in oral formulation, and penciclovir is available only as a 1% topical cream. Penciclovir and famciclovir seem to have greater in vitro activity against HSV and VZV compared with acyclovir.

Mechanism of Action

Penciclovir and the prodrug famciclovir are guanine nucleoside analogs, which exert their antiviral effects by incorporating into

growing DNA chains, subsequently interfering with viral DNA synthesis and replication.⁵³

Clinical Uses

Penciclovir has activity against viruses from the herpes family. It is effective against HSV-1, HSV-2, and VZV. Similar to acyclovir, it is less effective against EBV and CMV. In vitro studies have shown some activity against hepatitis B virus (HBV). Penciclovir and famciclovir are clinically used for the treatment of genital infections caused by HSV and VZV.

Adverse Reactions and Precautions

Penciclovir and famciclovir are considerably well tolerated. Use of famciclovir has been associated with nausea, vomiting, diarrhea, and headaches. Rare cases of neutropenia have been reported. Penciclovir is eliminated through the kidneys; therefore dosage adjustment of famciclovir is required in patients with moderate to severe renal insufficiency.⁵³

Ganciclovir and Valganciclovir

Ganciclovir is a guanine nucleoside analog with a mechanism of action similar to acyclovir. Valganciclovir is a newly approved prodrug of ganciclovir that improves ganciclovir absorption. Ganciclovir has a higher affinity for DNA transferase compared with acyclovir, which increases the intracellular half-life of the drug and allows for a less frequent regimen. Valganciclovir is available only in oral formulation; ganciclovir is available in oral, intravenous, and intraocular (eye implant) formulations.^{53,54}

Mechanism of Action

Ganciclovir and the prodrug valganciclovir are guanine nucleoside analogs. They have a similar mechanism of action as acyclovir.

Both agents incorporate into growing DNA chains, consequently terminating viral DNA synthesis and replication.^{53,54}

Clinical Uses

Ganciclovir resembles acyclovir in its activity against members of the herpes virus family and VZV. It has much higher activity against CMV in vitro and in vivo. Ganciclovir is indicated for the treatment and long-term suppression of CMV retinitis and prevention of CMV disease in patients with AIDS and in transplant recipients.^{53,54}

Adverse Reactions and Precautions

The most common adverse reaction associated with the use of ganciclovir is bone marrow suppression. In patients with AIDS, the incidence of thrombocytopenia and neutropenia may be 20% (thrombocytopenia) and 40% (neutropenia). Dosages should be reduced in the presence of renal insufficiency. In addition to the side effects of myelosuppression, headache, nausea, rash, fever, and liver transaminase elevations have been reported.^{53,54}

Cidofovir

Cidofovir is an acyclic phosphonate nucleoside analog that has potent antiviral activity against a wide variety of viruses. In contrast to the guanine nucleoside analogs, cidofovir has enhanced activity against HSV, EBV, VZV, and CMV. Cidofovir is available only as an intravenous formulation.^{53,54}

Mechanism of Action

Cidofovir exerts its mechanism of action by inhibition of viral replication. Cidofovir is phosphorylated and inserted into the growing DNA chain. Once inserted, viral replication is terminated by inhibition of viral polymerases.

Clinical Uses

Cidofovir has potent activity against members of the herpesvirus family, EBV and CMV. It is indicated for use in patients with CMV when previous treatment with ganciclovir or foscarnet has failed. It has been used extensively in the treatment of CMV retinitis in patients with AIDS.^{53,54}

Adverse Reactions and Precautions

Severe dose-dependent nephrotoxicity has been associated with the use of cidofovir. It is contraindicated in individuals with renal insufficiency. Saline infusions before and concomitant probenecid administration during cidofovir treatment have been used to reduce nephrotoxicity. In addition to nephrotoxicity, neutropenia, fever, headache, emesis, rash, and diarrhea have been reported with cidofovir use.^{53,54}

Foscarnet

Foscarnet is a pyrophosphonate nucleoside analog that has potent antiviral activity against HSV, EBV, VZV, and CMV. In addition, foscarnet has shown activity against HBV and influenza viruses. It is poorly absorbed, and it is available only as an intravenous formulation.^{53,54}

Mechanism of Action

Because foscarnet is a pyrophosphate analog, it does not require phosphorylation to become active. Foscarnet works by reversibly blocking viral polymerase phosphorylation, which inhibits viral replication.^{53,54}

Clinical Uses

Foscarnet has activity against herpesviruses, including VZV and EBV, and influenza A and B. Foscarnet is used mainly to treat CMV retinitis in patients with AIDS who are unable to tolerate ganciclovir therapy. It is also used for treatment of CMV infections in other individuals with immunosuppression (e.g., organ transplant recipients). In addition, foscarnet has been used to treat HSV and VZV infections that are resistant to acyclovir and ganciclovir. Ganciclovir or acyclovir may act synergistically with foscarnet against some strains of CMV.^{53,54}

Adverse Reactions and Precautions

Nephrotoxicity is a relatively common side effect that occurs in approximately 25% of patients treated. Adequate hydration during foscarnet infusion may reduce the incidence of nephrotoxicity. Dosage reduction is required in individuals with renal insufficiency. Other adverse reactions include fever, nausea, electrolyte imbalances, vomiting, diarrhea, and headache.^{53,54}

Amantadine and Rimantadine

Amantadine and rimantadine are closely related antiviral agents with activity against influenza A only. Both agents are well absorbed from the gastrointestinal tract and are suitable for oral administration.⁵³

Mechanism of Action

Amantadine and rimantadine act by inhibiting viral replication and viral assembly. It is also thought that these agents inhibit the influenza virus from uncoating and entering the mucosal cells of the respiratory tract.

Clinical Uses

Amantadine and rimantadine have a narrow spectrum of activity because they are active only against influenza A virus. Both agents may be used prophylactically in high-risk (i.e., immunocompromised) patients who are unable to tolerate or benefit from influenza vaccination. They may also be used in conjunction with vaccination in the same high-risk patient populations. To be effective, these agents should be initiated within the first 48 hours of onset of symptoms.⁵³

Adverse Reactions

Amantadine and rimantadine are well tolerated. Central nervous system side effects, such as tremor, insomnia, lightheadedness, seizure, cardiac arrhythmias, and agitation, have been reported with both drugs (more often with amantadine) and seem to be related to higher serum concentrations of these agents. A dosage adjustment of amantadine, but not rimantadine, is required in the presence of renal insufficiency.⁵³

Oseltamivir, Zanamavir, and Peramivir

Oseltamivir, zanamavir, and peramivir belong to the class of antivirals known as *neuraminidase inhibitors*. Oseltamivir is a prodrug that is converted to its active form (oseltamivir carboxylate) after it is absorbed. It is available only as an oral formulation. Zanamavir is structurally related to oseltamivir; however, it is administered by oral inhalation only. Peramivir is only available as an intravenous solution, and because of its differing chemical structure, it binds to influenza neuraminidase with a higher affinity compared with oseltamivir.^{53,55}

TABLE 14.11 COVID-19 Monoclonal Antibody Dose, Route, and Indication ^{64–68}

Monoclonal Antibody	Adult Dosage	Route	Indication
Bamlanivimab/etesevimab	700 mg/1400 mg	IV	• Post-exposure prophylaxis • Treatment of mild to moderate COVID-19
Casirivimab/imdevimab	600 mg/600 mg initial dose	IV or SubQ	• Post-exposure prophylaxis • Treatment of mild to moderate COVID-19
Sotrovimab	500 mg	IV	• Treatment of mild to moderate COVID-19
Tixagevimab/cilgavimab	300 mg/300 mg	IM	• Pre-exposure prophylaxis
Bebtelovimab	175 mg	IV	• Treatment of mild to moderate COVID-19

IM, Intramuscular; IV, intravenous; SubQ, subcutaneous.

Mechanism of Action

Oseltamivir, peramivir, and zanamavir specifically inhibit influenza A and B neuraminidase, which prevents influenza viruses from leaving the host cell to infect other cells.^{53,55}

Clinical Uses

Neuraminidase inhibitors are effective only for the treatment of influenza A and B infection. They have been shown clinically to reduce the duration of influenza infection. However, therapy must be initiated within 40 hours of the initiation of symptoms to be effective.⁵³

Adverse Reactions and Precautions

Oseltamivir and zanamivir are well tolerated; nausea and vomiting are reported as the most frequent adverse reactions. These symptoms usually occur on the first 2 days of therapy. Bronchospasm has been seen more frequently with zanamivir and appears to be related to the route of administration. The most commonly reported adverse events with peramivir are diarrhea, nausea, vomiting, insomnia, and hypertension. Dosage adjustment is required in patients with renal insufficiency.^{53,55}

Baloxavir Marboxil

Baloxavir marboxil is an antiviral that gained FDA approval in 2018 for influenza A and B treatment and post-exposure prophylaxis. Following administration, the baloxavir marboxil prodrug is hydrolyzed to the active drug baloxavir.^{56,57}

Mechanism of Action

Baloxavir marboxil prevents viral replication through inhibition of the endonuclease activity of the polymerase acidic (PA) protein. Administration of baloxavir marboxil inhibits gene transcription as the PA protein is a vital component of the viral RNA polymerase complex.^{56,57}

Clinical Uses

Effective against both influenza A and B, baloxavir marboxil should be started within 48 hours of symptom onset for treatment and as soon as possible following positive contact exposure for prophylaxis.^{56,57}

Adverse Reactions and Precautions

Baloxavir marboxil is typically well tolerated and most commonly reported side effects are diarrhea, nausea, and sinusitis.

All were only reported in 2% to 3% of patients taking baloxavir marboxil.^{56,57}

COVID-19 Antivirals. Since the first reported cases of COVID-19 infection were reported in December of 2019, a significant amount of effort has been directed at identifying potentially useful pharmacologic agents to aid in the prevention and treatment of this worldwide pandemic. At this writing, there are a number of clinically effective agents available to treat COVID-19 at its various stages of infection, with more in the pipeline. Like any novel infectious process, new and continually updated clinical data will be available once scientists are able to analyze the current research studies.

Remdesivir. Remdesivir is an antiviral agent with activity against COVID-19 and other RNA viruses. Initially developed for use as a potential therapeutic modality during a global viral pandemic, recent testing demonstrated remdesivir displayed significant in vitro activity against COVID-19.⁵⁸

Mechanism of Action

Remdesivir is formulated as a prodrug and is metabolized to adenosine triphosphate. Once metabolized, remdesivir binds and inhibits RNA-dependent RNA polymerase causing termination of viral transcription.⁵⁸

Clinical Uses. Current guidance set forth by the Infectious Diseases Society of American conditionally recommends the use of remdesivir for use in hospitalized patients with moderate or high-risk of disease progression versus no antiviral. In addition, use can also be considered in those ambulatory patients who are at high risk for COVID-19 disease progression. Ideally, treatment should be initiated as close to the development of COVID-19 symptoms and continued twice daily for 5 days.⁵⁸

Adverse Reactions and Precautions. While the data are limited, remdesivir appears to be fairly well tolerated. Clinical studies have reported rare cases of infusion-related reactions, anaphylaxis, and hypersensitivity reactions. More commonly reported adverse reactions appeared to be gastrointestinal, as well as elevations in transaminases. It is important to remember, remdesivir is eliminated primarily through the kidneys; therefore, renal dose adjustment is necessary in patients with CrCl < 30 ml/min.⁵⁹

Molnupiravir and Nirmatrelvir/Ritonavir

Molnupiravir and nirmatrelvir/ritonavir are recently approved oral agents through an FDA-issued EUA (Emergency Use Authorization) for the treatment of COVID-19 in ambulatory patients at high risk for disease progression. Unlike their predecessor

remdesivir, both molnupiravir and nirmatrelvir/ritonavir are only available in oral formulations.^{60,61}

Mechanism of Action. Similar to remdesivir, molnupiravir targets RNA replication in COVID-19, while nirmatrelvir/ritonavir acts by inhibiting an essential protease responsible for processing COVID-19 polypeptides involved in viral replication. Because of the extensive metabolism of nirmatrelvir by CYP 3A4, it is necessary to co-formulate with ritonavir to inhibit the metabolism.^{60–62}

Clinical Uses. Molnupiravir and nirmatrelvir/ritonavir are only indicated for use in those individuals with COVID-19 who are at moderate to high-risk disease progression. Therapy should be initiated within 5 days of symptom onset.^{60–62}

Adverse Reactions and Precautions. Due to the co-formulation of nirmatrelvir with ritonavir, there is the potential for drug interactions in patients receiving other medications metabolized through the CYP 3A4 system. In addition, careful monitoring of renal function is necessary if this agent requires dose reducing with CrCl < 30 ml/min. Common side effects appear mild and typical presented as gastrointestinal (diarrhea and dysgeusia). In contrast to nirmatrelvir/ritonavir, molnupiravir had significantly less drug interactions; however, concerns of potential teratogenicity have caused the FDA to not recommend its use in pregnancy and recommend those individuals of child-bearing potential use contraception during and at least 4 days after treatment with molnupiravir.^{60–62}

Biologics

KEY POINT

Biologics are substances synthesized from living systems. Monoclonal antibodies are a category of biologics that are currently being utilized to treat a variety of immune disorders, neoplasms, psoriasis, multiple sclerosis, and rheumatoid arthritis. Most recently, several antibacterial monoclonal antibodies are under development to target infectious pathogens. Antibacterial monoclonal antibodies that are currently licensed target exotoxins, but mechanisms under development include targeting cell surface components in an effort to facilitate bactericidal clearance.⁶³

COVID-19 and Monoclonal Antibodies

Monoclonal antibodies are another evolving COVID-19 prevention and treatment modality. The monoclonal antibodies directly target the SARS-CoV-2 spike protein, blocking viral attachment and entry into human cells. Monoclonal antibody treatment is primarily reserved for patients at high risk for developing severe disease due to immune compromise, immunosuppressive therapies, or inadequate COVID-19 immunization response. Bamlanivimab/etesevimab and casirivimab/imdevimab were among the first monoclonal antibody combinations issued EUAs for COVID-19 prophylaxis and/or treatment.^{64,65} Sotrovimab, tixagevimab/cilgavimab, and bebtelovimab quickly gained EUAs, offering alternative and/or additional variant coverage.^{66–68} Table 14.11 lists monoclonal antibodies under EUA at the time of this writing. Similar to other biologics, most common side effects observed are infusion related in nature.

Raxibacumab and Obiltoxaximab

Raxibacumab and obiltoxaximab are approved for adult and pediatric postexposure treatment of *Bacillus anthracis* inhaled anthrax

in conjunction with a recommended antimicrobial agent. Both monoclonal antibodies are also approved for inhalation anthrax preexposure prophylaxis when alternative therapies are inappropriate or unavailable.⁶⁹

Mechanism of Action

Raxibacumab and obiltoxaximab are both human immunoglobulin G1 monoclonal antibodies that bind to and neutralize the protective antigen of *B. anthracis*. The agents inhibit the active lethal factor and edema factor from entering the cytoplasm and exerting toxic effects, earning them their identity of “anthrax antitoxins.”⁶⁹

Clinical Uses

In combination with an appropriate antimicrobial agent, such as fluoroquinolones, tetracyclines, or penicillin G, raxibacumab, and obiltoxaximab antitoxins are approved for postexposure treatment of *B. anthracis* inhalation anthrax. In the absence of appropriate alternative therapies, either monoclonal antibody may be used for preexposure prophylaxis of anthrax caused by inhalation of *B. anthracis*.⁶⁹

Adverse Reactions and Precautions

Because of the risk of a hypersensitivity reaction to raxibacumab and obiltoxaximab, patients should be premedicated with diphenhydramine before the monoclonal antibody infusion. The most common adverse effects reported with these agents are pruritus, headache, upper respiratory tract infection, and cough.⁶⁹

RESPIRATORY CARE ASSESSMENT OF ANTIBIOTIC THERAPY

Before Treatment

- Assess effectiveness of drug therapy on the basis of indications for the agent (i.e., virus or bacteria).

During Treatment and Short Term

- Consider susceptibility testing.
- Assess effectiveness of current agents.

Long Term

- Monitor response to therapy.
- Consider combination of agents.

General Contraindications

- Antimicrobials should not be used unless a specific pathogen is known or suspected to avoid development of drug resistance.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What is the difference between bacteriostatic and bactericidal antimicrobial agents?
2. Give an example of a class of antimicrobials that kill in a concentration-dependent manner *and* in a concentration-independent manner.
3. Describe at least three parameters that may indicate antibiotic failure in a patient.
4. Why is combination antibiotic therapy useful? (Be specific.)

- Describe the mechanism of action of penicillin antibiotics. Name at least two additional antibiotic classes with similar mechanisms of action.
- Which β -lactam antibiotic is least likely to cause an allergic reaction in a patient with a penicillin allergy?
- Name three antimicrobial agents that would be useful in the treatment of community-acquired pneumonia (CAP).
- What is the antimicrobial agent of choice for treatment of *Pneumocystis pneumonia* (PCP)?
- What agents are considered first-line therapy for treatment of pulmonary tuberculosis?
- Which antimicrobial agents are useful for the treatment of nosocomial pneumonia caused by *Pseudomonas aeruginosa*?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

Chief Complaint

Jackson Daniels, a 64-year-old White male, has presented to the Community Hospital with complaints of fever, cough, and shortness of breath. He states that he has been coughing up “thick, greenish mucus.”

History of Present Illness

Mr. Daniels states that he has been feeling bad for over a week but that his symptoms had gotten much worse a couple of days ago. He had gone to an Urgent Care Center and was given azithromycin, guaifenesin, and an albuterol inhaler; however, his symptoms did not improve, and he was still having fevers and productive cough, and the inhaler was not helping his breathing.

Past Medical History

- Chronic alcohol abuse, with several admissions in the past for alcohol withdrawal (delirium tremors)
- Chronic obstructive pulmonary disease (COPD) with multiple hospital admissions for COPD exacerbation
- Recurrent pneumonia, including methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia
- Gastroesophageal reflux disease (GERD)

Social History

- Divorced with no children; unable to work because of poor health

Tobacco/Alcohol/Substance Use

- Tobacco history: 1 pack per day (ppd) for over 40 years
- Alcohol: 6 to 8 cans of beer daily
- Substance use: Denies use of illicit drugs.

Allergies

- Penicillin (rash), sulfa (rash and gastrointestinal [GI] upset)

Home Medications

- Azithromycin 500 mg orally (PO) daily for 1 day, then 250 mg PO daily for 4 days (2 tablets remaining)
- Guaifenesin ER 1200 mg PO twice daily
- Albuterol metered dose inhaler (MDI) 2 puffs as needed (PRN) q4-6h
- Over the counter (OTC) Prilosec 20 mg PO twice daily (GERD)
- Duonebs (albuterol-ipratropium) inhaled four times daily (qid) (COPD)

Physical Examination

- General:** Breathing fast; appears in moderate to severe respiratory distress
- Head, ears, eyes, nose, throat (HEENT):** Pupils equally round and reactive to light and accommodation (PERRLA), denies headache, no sore throat or nasal discharge

- Cardiovascular:** Tachycardic with a regular rhythm. No murmurs, rubs, or gallops
- Pulmonary:** Bilateral crackles, worse on left side; decreased breath sounds over lower left lobe
- GI, genitourinary (GU), musculoskeletal, skin, neurologic:** Unremarkable

Vital Signs

- Temperature (T) 102.2°F
- Blood pressure (BP) 150/85 mm Hg
- Heart rate (HR) 105 beats/min
- Respiratory rate (RR) 29 breaths/min
- Oxygen saturation by pulse oximetry (SpO₂) 90% on 2 L oxygen (O₂), 82% on room air
- Weight 185 lb
- Height 70 inches

Laboratory/Radiographic Tests

- White blood cell (WBC) count:** 18.4×10^3 cells/mm³
- Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]):** Moderately elevated
- Sputum Gram stain:** Many WBCs, few epithelial cells, many gram-positive cocci in clusters
- Sputum culture:** Pending
- Chest x-ray (CXR):** Left lower lobe infiltrate

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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15

Cold and Cough Agents

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CHAPTER OUTLINE

Sympathomimetic (Adrenergic) Decongestants

- Topical Application
- Systemic Application

Antihistamine Agents

- Effect of Histamine
- Histamine Receptors
- Antihistamine Agents
- Effects of Antihistamines
- Structure–Activity Relationships
- Use With Colds
- Treatment of Seasonal Allergic Rhinitis

Expectorants

- Efficacy and Use
- Use in Chronic Bronchitis
- Mechanism of Action

Expectorant Agents

- Iodine Products
- Guaifenesin (Glycerol Guaiacolate)
- Topical Agents
- Parasympathomimetics (Cholinergic Agents)

Cough Suppressants (Antitussives)

- Agents and Mechanism of Action
- Use of Cough Suppressants

Cold Compounds

- Treating a Cold

Respiratory Care Assessment of Cold and Cough Agents

- Before Treatment
- During Treatment and Short Term
- Long Term
- General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to cold and cough agents
2. Differentiate between the common cold and the flu
3. Differentiate between the specific types of cold and cough agents
4. Discuss the mechanism of action for each specific cold and cough agent

KEY TERMS AND DEFINITIONS

Antihistamines Drugs that reduce the effects mediated by histamine, a chemical released by the body during allergic reactions. Antihistamines are often administered to reduce secretions (e.g., runny nose and sneezing), but they can cause drowsiness and impaired responses. *Note:* Drying of secretion, whether caused by antimuscarinic or antihistamine action, may suppress a needed defense reaction of the airways. Nocturnal use is indicated more than around-the-clock use.

Antitussives Drugs that suppress the cough reflex. *Note:* Productive coughs should not be suppressed; the rationale behind an expectorant–antitussive combination is questionable.

Common cold Nonbacterial respiratory tract infection, generally caused by a viral infection of the epithelial layer of the upper airway and characterized by malaise, low-grade fever, cough, sneezing, and a runny nose.

Expectorants Drugs that increase the stimulation of mucus. Many have questionable efficacy in a cold. The best expectorant,

especially with colds, is plain water and juices, avoiding caffeinated beverages, such as tea or colas, and beer or other alcoholic mixtures.

Flu Nonbacterial infection with rapid onset of symptoms, including fever, headache, and fatigue.

Mucokinesis Therapeutic movement of excessive or abnormal secretions from the respiratory tract.

Mucolytic expectorants Agents that facilitate removal of mucus by a lysing, or mucolytic, action. *Example:* dornase alfa.

Stimulant expectorants Agents that increase the production and presumably the clearance of mucus secretions in the respiratory tract. *Example:* guaifenesin.

Sympathomimetics Drugs that partially or completely mimic the effects of the sympathetic nervous system. *Note:* Tremor, tachycardia, and increased blood pressure can occur with use of sympathomimetics, especially when taken orally. Rebound congestion can occur if used for longer than a day.

Large numbers of compounds are available, both by prescription and over the counter (OTC), for treating symptoms of the common cold. The term **common cold** is used to describe nonbacterial upper respiratory tract infections (URIs), usually characterized by mild general malaise and a runny, stuffy nose. Other symptoms include sneezing, cough, and possibly a sore throat or some chest discomfort. Allergic rhinitis and serious illnesses, such as influenza, acute bronchitis, and infections of the lower respiratory tract, are not included in this discussion. Influenza, or the **flu**, is caused by the influenza virus and is associated with symptoms of fever, headache, general muscle ache, and extreme fatigue or weakness. Onset of symptoms is usually rapid. The fever and systemic symptoms of influenza are contrasted with symptoms of the common cold in [Table 15.1](#).

Four classes of agents can be distinguished in cold remedies, used individually or in combination, as follows:

- **Sympathomimetics:** For decongestion
- **Antihistamines:** To reduce (dry) secretions
- **Expectorants:** To increase mucus clearance
- **Antitussives:** To suppress the cough reflex

The previously listed four classes of cold medications target the primary symptoms caused by the cold virus in the respiratory tract; this is illustrated conceptually in [Fig. 15.1](#). Each class is discussed subsequently, with representative agents listed. In addition to these four types of ingredients, an analgesic, such as acetaminophen, may be included in a cold medication, as in Sinutab, which consists of 30 mg of pseudoephedrine (decongestant) and 325 mg of acetaminophen (analgesic).

Sympathomimetic (Adrenergic) Decongestants

CLINICAL CONNECTION

Adrenergic agents act to reduce swelling and relieve nasal congestion. Pseudoephedrine (Sudafed) is a common agent used for its α properties (causing vasoconstriction).

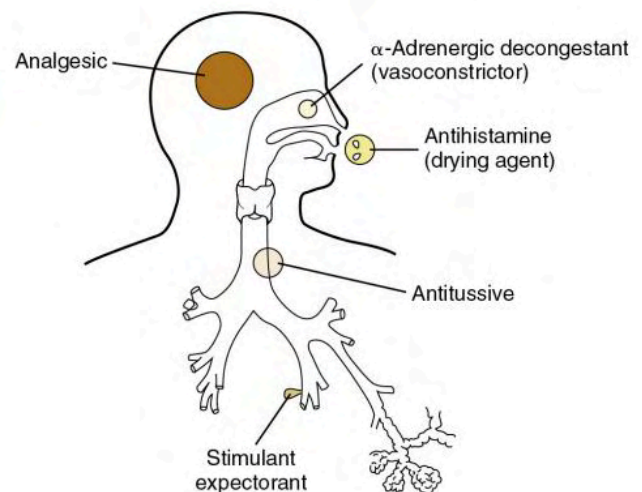
Sympathomimetic (adrenergic) agents are discussed as bronchodilators in [Chapter 6](#), and the general effects of sympathetic

stimulation are outlined in [Chapter 5](#). In cold remedies, sympathomimetics are intended for a decongestant effect, which is based on their α -stimulating property and resulting vasoconstriction.

Sympathomimetics, such as pseudoephedrine, are sold under brand names, such as Sudafed, and can be taken orally. Because of changes in the USA PATRIOT Act (Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001), single agents or combination drugs using pseudoephedrine are placed behind the counter in pharmacies, and regulated sales are documented because the drug has been purchased excessively for the illegal production of methamphetamines. Manufacturers have turned to phenylephrine as a substitute; however, the 10-mg dose that has been approved by the US Food and Drug Administration (FDA) has little effect on nasal decongestion when used orally because of the drug's high first-pass effect. In a meta-analysis by Hatton et al.,¹ it was found that 10 mg of phenylephrine was no more effective than a placebo. Oxymetazoline, a sympathomimetic, sold under such brand names as Afrin and Vicks Sinex, can be used topically on the nasal mucosa. Topical applications generally require lower dosages compared with oral use. Problems can occur with either route of administration. [Table 15.2](#) lists sympathomimetic agents used as nasal decongestants in cold remedies.

Topical Application

Topical sympathomimetic decongestant sprays or drops produce results faster compared with oral applications. However, repeated use of these agents can cause a vicious cycle of increased secretions



• **Fig. 15.1** Cold medications include four classes of drugs targeted at the symptoms produced by this upper respiratory viral infection, along with analgesics.

TABLE 15.1 Differences in Symptoms Between the Common Cold and Influenza

Signs and Symptoms	Cold	Influenza
Chills	None	Typical
Cough	Present, hacking	Nonproductive, may be severe
Fatigue	Mild	Early and severe
Fever	Rare	Typical, high
Headache	Rare	Prominent
Myalgia	None or slight	Usual, may be severe
Nasal congestion	Common	Occasional
Sore throat	Common	Occasional
Sneezing	Common	Occasional

TABLE 15.2 Examples of Adrenergic Agents Used as Nasal Decongestants

Drug	Route
Naphazoline (Privine)	Topical
Oxymetazoline (Afrin)	Topical
Phenylephrine (Sudafed PE)	Topical, oral
Pseudoephedrine hydrochloride (Sudafed, various)	Oral

and nasal edema as the effect of the agent fades. This condition is referred to as *rebound congestion* and can cause the patient to become addicted to the agent and use it repeatedly. In rebound congestion, nasal vasoconstriction does not occur, and the nasal mucosa swells.

KEY POINT

Adrenergic decongestants are useful for nasal clearing, but rebound congestion can occur.

Systemic Application

Systemic (in comparison with topical) application has the advantage of giving more extensive decongestant effects involving deeper blood vessels. Production of nasal vasoconstriction through systemic routes, however, often leads to other systemic effects of sympathomimetics, such as an increase in blood pressure and in heart rate.

Antihistamine Agents

Histamine occurs naturally in the body and is contained in tissue mast cells and blood basophils. The role of the mast cell in releasing histamine with allergic asthma is discussed in [Chapters 11 and 12](#).

Effect of Histamine

Histamine is an important mediator of local inflammatory responses that causes such effects as smooth muscle contraction, increased capillary permeability and dilation, itching, and pain. Scraping a tongue depressor or blunt pencil across the sensitive skin of the inner arm can illustrate a local inflammatory reaction at least partly mediated by histamine. The result is a wheal-and-flare reaction, also called a “triple response” (local redness, welt formation, and a reddish-white border). The redness and wheal (“welt”) are caused by dilation and leakage of plasma proteins from skin capillaries. The exudation of plasma causes the swelling. The flare, or the reddish-white area surrounding the wheal, is probably caused by local axon reflexes from sensory fibers causing dilation of neighboring arterioles.

Histamine Receptors

Histamine produces its inflammatory effects by stimulating specific cell surface receptors. Three types of histamine (H) receptors have been discovered. Two of the receptors are distinguished in mediating local inflammatory responses. The three histamine receptors are as follows:

1. *H₁ receptors*: Located on nerve endings and smooth muscle and glandular cells. *H₁* receptors are involved in inflammation and allergic reactions, producing wheal and flare reactions in the skin, bronchoconstriction and mucus secretion, nasal congestion and irritation, and hypotension in anaphylaxis.²
2. *H₂ receptors*: Located in the gastric region. *H₂* receptors regulate gastric acid secretion and feedback control of histamine release.²
3. *H₃ receptors*: Located primarily in the central nervous system (CNS). *H₃* receptors may be autoreceptors for cholinergic neurotransmission in the airway at the autonomic ganglia, which

are involved in CNS functioning and feedback control of histamine synthesis and release.^{2,3}

The typical antihistamine found in cold medications is an *H₁*-receptor antagonist. Examples of these are pyrilamine and chlorpheniramine. *H₁*-receptor antagonists block the bronchopulmonary and vascular actions of histamine to prevent rhinitis and urticaria.⁴ *H₂*-receptor antagonists are used to block gastric acid secretion when treating ulcers. Examples of *H₂*-receptor antagonists are cimetidine (Tagamet) or ranitidine (Zantac). Currently, *H₃* receptors are under investigation; no FDA-approved agents are available in the United States.

Antihistamine Agents

KEY POINT

Antihistamines dry secretions through an anticholinergic effect and by blockade of histamine 1 (*H₁*) receptors.

All of the antihistamines discussed in this chapter are *H₁*-receptor antagonists. These antihistamine agents are classified further into the major groups listed in [Table 15.3](#). The first five groups of antihistamines listed in [Table 15.3](#); all are first-generation agents and can be found in cold preparations. Some of the brand names given may be familiar from OTC preparations readily available in drugstores. Others are found in combination products; these are discussed and listed subsequently. Second-generation antihistamines, which are longer acting and nonsedating, are also listed in [Table 15.3](#).

TABLE 15.3 Major Groups of Antihistamines With Representative Agents by Nonproprietary and Brand Names

Group	Drug
First Generation (Nonselective)	
Alkylamine derivatives	Chlorpheniramine (Chlor-Trimeton) Brompheniramine Dexchlorpheniramine maleate
Ethanolamine derivatives	Diphenhydramine HCl (Benadryl) Clemastine (Tavist) Carbinoxamine
Phenothiazine derivatives	Promethazine HCl
Piperazine	Hydroxyzine (Vistaril)
Piperidine derivatives	Cyproheptadine
Second Generation (Peripherally Selective)	
Nonsedating, Long Acting	
Phthalazinone	Azelastine (Astelin, Astepro)
Piperazine	Cetirizine (Zyrtec) Levocetirizine (Xyzal) Olopatadine (Patanase)
Piperidines	Loratadine (Claritin) Fexofenadine (Allegra) Desloratadine (Clarinex)

Effects of Antihistamines

Antihistamines have three major classes of effects: antihistaminic, sedative, and anticholinergic activity. Second-generation agents are selective for H_1 receptors and are less sedating than first-generation agents. Antihistaminic activity blocks the increased vascular permeability, pruritus, and bronchial smooth muscle constriction caused by histamine. These actions are the reason antihistamines are used to treat allergic disorders, such as rhinoconjunctivitis, allergic rhinitis, and urticaria.

The sedative effect of antihistamines is thought to be caused by penetration of the agents into the brain, where inhibition of histamine *N*-methyltransferase and blockage of central histaminergic receptors occurs. There is also antagonism of other CNS receptors, such as serotonin and acetylcholine.² The effect of drowsiness with first-generation (older) antihistamines can be a major hazard if alertness is required, such as in operating heavy machinery (e.g., a car) or monitoring a patient. This effect can be so pronounced that diphenhydramine hydrochloride (HCl) is added to acetaminophen in Tylenol PM, and the compound is described as a non-prescription sleep aid.

Finally, the anticholinergic effect produces considerable upper airway drying, just as would occur with an antimuscarinic agent, such as atropine sulfate. In addition, effects seen with cholinergic blockade may occur, including CNS effects of stimulation, anxiety, and nervousness and peripheral effects of dilated pupils, blurred vision, urinary retention, and constipation.³ These effects are less likely in occasional use with a cold, but they may be significant with greater use (and dose) for allergic rhinitis or other conditions (e.g., urticaria).

CLINICAL CONNECTION

Antihistamines dry secretions but can cause impaction of secretions and possible sinus blockage and should be used sparingly. Use during work should be avoided because of drowsiness occurring as a side effect.

The duration of action of older antihistamines is generally 4 to 6 hours. However, newer, second-generation agents, often termed “nonsedating,” are effective for 12 hours or more, depending on the

dose, and do not have sedating and anticholinergic effects. Examples of these newer agents are fexofenadine (Allegra) and cetirizine (Zyrtec) (see Table 15.3). Second-generation agents have little affinity for muscarinic cholinergic receptors and therefore do not cause dry mouth or gastrointestinal side effects. They also lack anti-serotonin activity and do not cause appetite stimulation and weight gain, although astemizole and ketotifen may differ in this.³ These newer drugs may inhibit mediator release from allergic inflammatory cells in addition to blocking the histamine receptor. Allergic symptoms of sneezing and rhinorrhea are equally well controlled with first-generation and second-generation H_1 antagonists.³

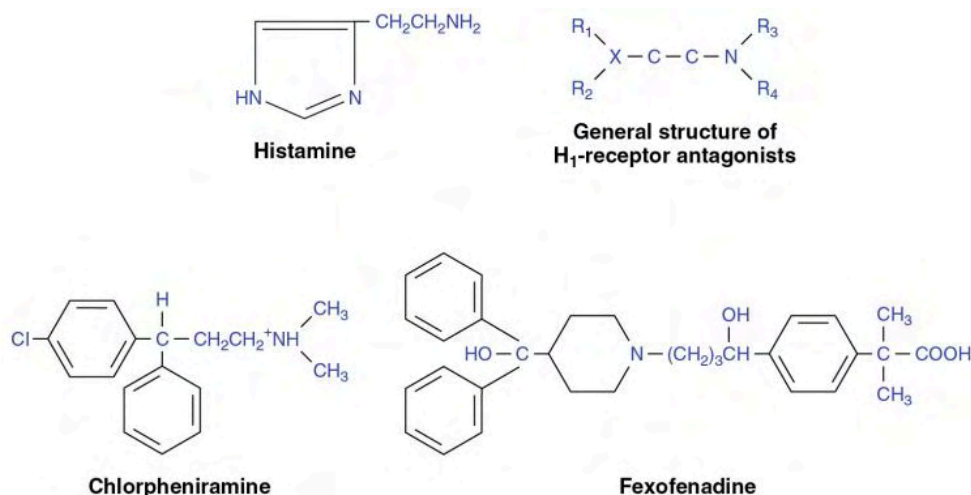
Structure–Activity Relationships

H_1 -receptor antagonists were first discovered in 1937.⁴ The chemical structure of histamine, the general structure of H_1 -receptor antagonists, and two examples of H_1 -receptor antagonists are shown in Fig. 15.2. Chlorpheniramine is an antihistamine found in many cold remedies; it represents one of the older, classic H_1 -receptor antagonists. Fexofenadine is a newer, nonsedating H_1 -receptor antagonist.

The resemblance between histamine and the general formula for the H_1 -blocking agents can be seen in the structures shown. In older agents, exemplified by chlorpheniramine, R_1 and R_2 attachments are usually a ring structure connected to an ethylamine (C–C–N) group. The presence of the ring structures and other substitutions on the structure makes older antihistamines lipophilic. As a result, classic first-generation antihistamines readily penetrate the CNS and produce the effect of sedation and drowsiness previously discussed. Newer, nonsedating agents, such as terfenadine, do not readily cross the blood–brain barrier and therefore do not block central H_1 receptors.⁴

Use With Colds

A beneficial effect of antihistamine use with a cold is the drying of upper airway secretions, which lessens the rhinitis and accompanying sneezing. There is some question whether the drying of secretions results from histamine antagonism or to the



• **Fig. 15.2** Structure of histamine (H), an inflammatory mediator; the general structure of H_1 -receptor antagonists; and the structure of two antihistamines, chlorpheniramine and fexofenadine, are shown. R_1 to R_4 (Ring Structures 1–4) indicate the sites of attachments, with R_1 and R_2 (Ring Structures 1 and 2) being ring structures in most H_1 antagonists.

anticholinergic effect of these agents. How much histamine release occurs with colds is debated. In allergic rhinitis, there is no question that histamine causes much of the inflammatory response, and the newer long-acting agents are particularly helpful with this condition. Blockade of H_1 receptors prevents histamine's contribution to symptoms, such as nasal itching, congestion, sneezing, rhinorrhea, and ocular irritation.

Regardless of the exact effect, the drying of runny nasal secretions is welcomed by individuals with a cold, and the drying of secretions coupled with drowsiness can be useful to produce the needed rest and sleep at night. Secretion, however, is a defense mechanism triggered by an upper airway viral infection. Antihistamines may cause harm because of suppressed secretion clearance and impacted secretions with sinus blockage.⁴ Adequate hydration with a cold is always helpful, with or without use of antihistamines.

An alternative to antihistamines for rhinorrhea in a cold is the anticholinergic nasal spray ipratropium bromide, which is discussed in Chapter 7. Ipratropium has been shown to be effective in reducing nasal discharge in viral infectious rhinitis (colds) and allergic and nonallergic rhinitis.⁵ There is no evidence of rebound congestion, mucosal irritation, or significant systemic effects. Ipratropium can be effective for 4 to 8 hours. An anticholinergic agent applied topically offers an attractive alternative to vasoconstricting decongestants and antihistamine H_1 antagonists.

Treatment of Seasonal Allergic Rhinitis

Second-generation H_1 -receptor antagonists are more useful in the treatment of seasonal allergic rhinitis and other disorders requiring antihistamine treatment than in the treatment of colds. They are also better tolerated in treating allergic rhinitis compared with the first-generation agents because drowsiness is minimal, and the duration of action is longer. Such agents as astemizole, loratadine, fexofenadine, and cetirizine are indicated for use in seasonal allergic rhinitis and chronic urticaria. They are intended to relieve symptoms, such as sneezing; rhinorrhea; itchy nose, palate, and throat; itchy, watery eyes; and pruritus. Table 15.4 lists the categories and examples of agents used in the treatment of seasonal allergic rhinitis.⁶ Other uses of antihistamines include the treatment of symptoms occurring with motion sickness and control of nausea.

Expectorants

Expectorants are defined as agents that facilitate removal of mucus from the lower respiratory tract. A distinction is made in Chapter 9 between the following types of expectorants:

TABLE 15.4 Categories of Agents Used to Treat Seasonal Allergic Rhinitis

Category	Example
Anticholinergics	Ipratropium bromide
Corticosteroids	Budesonide, ciclesonide
Histamine 1 (H_1)-receptor antagonists	Cetirizine
Mediator antagonist	Cromolyn sodium
Specific immunotherapy	Standardized extracts
Vasoconstrictors	Pseudoephedrine

- **Mucolytic expectorants:** Agents that facilitate removal of mucus by a lysing, or mucolytic, action (*example:* dornase alfa).
- **Stimulant expectorants:** Agents that increase the production and presumably the clearance of mucus secretions in the respiratory tract (*example:* guaifenesin).

Generally, the expectorants considered here are stimulant expectorants, although the action does not always allow clear distinction. An example is guaifenesin, which is thought to reduce the adhesiveness and surface tension of mucus and increase **mucokinesis**—that is, movement and clearance of the secretion.

Efficacy and Use

There is controversy over the effectiveness and use of expectorants. The issue is caused by the following:

- Difficulty in assessing the effectiveness of expectorants, particularly because of lack of objective criteria to show effectiveness.
- In conjunction with the first point, it is difficult to determine who would benefit from the use of expectorants. Should expectorants be included in the treatment of cold symptoms if the cold involves the upper respiratory tract?

KEY POINT

Expectorants stimulate mucus production, and cough suppressants depress the cough reflex.

CLINICAL CONNECTION

The use of expectorants is questionable in an uncomplicated cold because the lower respiratory tract is not involved.

Use in Chronic Bronchitis

Petty⁷ reported the results of a national study evaluating use of the expectorant iodinated glycerol (Organidin). Patients had chronic bronchitis, which is quite different from the common cold. The study concluded that in chronic obstructive bronchitis, iodinated glycerol was safe and effective. Its use improved cough symptoms, chest discomfort, ease in bringing up sputum, and sense of well-being. The duration of acute exacerbations of chronic bronchitis was decreased. It is reasonable that in bronchitis, symptoms and airflow improve and further infection is reduced if mucus clearance can be improved. However, Rubin et al.⁸ found no change in lung function or sputum in patients with chronic bronchitis who used expectorants.

Irwin et al.⁹ published evidence-based guidelines in the diagnosis and management of cough. The guidelines cover acute and chronic cough and specific diseases, such as chronic bronchitis and cystic fibrosis (CF). (The specific guidelines can be accessed at [https://journal.chestnet.org/article/S0012-3692\(15\)52825-0/fulltext](https://journal.chestnet.org/article/S0012-3692(15)52825-0/fulltext).)

Mechanism of Action

Stimulant expectorants are thought to work by various means, depending on the agent. The mechanisms include the following:

- Vagal gastric reflex stimulation
- Absorption into respiratory glands to increase mucus production directly
- Topical stimulation with inhaled volatile agents

Guaifenesin, also known as *glycerol guaiacolate*, is classified as a category I agent, which means it is safe and effective.¹⁰ Ziment¹¹

reviewed the mechanisms of action with iodides, such as iodinated glycerol. Other agents, such as terpin hydrate, sodium citrate, ammonium chloride, and menthols, have no demonstrated efficacy.¹⁰

Because mucus incorporates water as it is produced, an adequate intake of plain water or other nondiuretic liquids (milk, fruit juices) can help preserve normal mucus viscosity and clearance, especially with a simple cold.

Expectorant Agents

Table 15.5 lists available expectorant agents. Major agents or groups of agents are briefly characterized.

Iodine Products

Potassium iodide is a very old agent that has been used as an expectorant in asthma and chronic bronchitis.¹² It has a direct mucolytic effect in sufficient concentrations. It also has an indirect effect on mucus viscosity by stimulating submucosal glands to produce new, lower viscosity secretions.

The exact mechanism of action with iodine products is unclear. Iodide appears to distribute to mucous glands, where it is secreted along with increased mucus. Iodide also stimulates the gastropulmonary reflex, has a mucolytic effect, and can stimulate ciliary activity.¹¹ Iodides are associated with hypersensitivity reactions in some individuals, and a case of pulmonary edema has been reported with its use.¹³

Guaifenesin (Glycerol Guaiacolate)

Guaifenesin taken via inhalation is also considered to be an emollient. In experimental animals, doses larger than those used in humans caused an increase in bronchial secretions. Guaifenesin taken orally is thought to reduce the adhesiveness and surface tension of mucus secretions, enhancing mucus clearance. It is approved by the FDA as being safe and effective.

Topical Agents

Topical agents usually evoke memories of the heated humidifier (vaporizer) with clouds of steam scented with camphor, menthol, or (in the past) chloroform. These agents may still be found in use, but efficacy as expectorants has not been shown. The burn risk of a hot vaporizer should preclude its use in children and in old or debilitated individuals.

Some research has shown that so-called bland aerosols of saline do increase sputum volume, possibly through reflex irritation of the bronchi and with increased secretion clearance as a result of coughing.¹⁴ A particulate suspension may have the potential to function as an irritant to the upper airways.

Parasympathomimetics (Cholinergic Agents)

Using parasympathomimetic agents stimulates mucous gland secretion, but the effect on other muscarinic receptors is too

diffuse for practical use as an expectorant. For this reason, such a drug as pilocarpine is not used as an expectorant. Likewise, stimulation of the medulla can increase respiratory tract secretions, but stimulation of the CNS is hazardous (see discussion on CNS stimulants in Chapter 20).

Cough Suppressants (Antitussives)

CLINICAL CONNECTION

Cough suppressants are useful for the treatment of a nonproductive, irritating, dry, hacking cough.

A fourth category of drugs used with colds and cold symptoms comprises cough suppressants. Coughing is a defense mechanism to protect the upper airway from irritants, such as dust particles, aerosols, liquids, and other foreign objects. This mechanism is a reflex, coordinated by a postulated cough center in the medulla. Detailed guidelines for cough management are provided by Irwin et al.⁹

Agents and Mechanism of Action

Cough suppressants act by depressing the cough center in the medulla. Narcotics (see Chapter 20) exert powerful depressant effects on the medullary centers, including the carbon dioxide chemoreceptors, and are often used for this purpose. Common agents are codeine or hydrocodone. A commonly used nonnarcotic drug is dextromethorphan.

Benzonatate (Tessalon), a nonnarcotic agent, is chemically related to the local anesthetic tetracaine and anesthetizes stretch receptors in the lungs and the pleura; this inhibits the cough reflex at its source. There is no inhibitory effect on the CNS. The effect begins in 15 to 20 minutes and lasts 3 to 8 hours.¹⁵ The antihistamine diphenhydramine (Benadryl), available as a syrup and in combination with other products, may be an effective cough suppressant. Diphenhydramine is becoming more common in products because of increased abuse of dextromethorphan. It should be noted that individuals taking any agent with diphenhydramine should be warned of the effect of drowsiness.

CLINICAL CONNECTION

The use of opioids as an antitussive can result in reduction of breathing.

Some cough suppressants, or antitussives, contain codeine. In a dose less than 15 mg, codeine does not produce analgesia in an adult. In the 10- to 20-mg range, there is an antitussive action. At doses greater than 30 mg, codeine produces analgesia. Hydrocodone produces an antitussive effect with a dose of approximately 5 mg. Box 15.1 lists common antitussive agents, many of which are used in cold compounds. Dextromethorphan and codeine

TABLE 15.5 Partial List of Expectorants

Drug	Representative Brand
Guaifenesin (glycerol guaiacolate)	Robitussin, Mucinex
Iodinated glycerol	Ilophen, Par Glycerol, R-Gen
Potassium iodide	SSKI, Pima

• BOX 15.1 Cough Suppressant Drugs

Benzonatate (Tessalon)
Codeine sulfate (various brand names)
Dextromethorphan (Delsym, Trocal, Robitussin Maximum Strength Cough)
Diphenhydramine (various brand names)
Hydrocodone (Tussionex Pennkinetic)

are the preferred cough suppressants because of their safety and efficacy. However, prescription for an antitussive, especially for a cold, is unusual because of the easy availability of OTC preparations. Codeine is available over the counter in some states and is not regulated by the FDA when it is present in low doses, as in OTC preparations. Codeine is a state-regulated drug, which is placed behind the counter if the particular state allows its use. In 2018, the FDA requires that prescription of all cold and cough agents containing opioids (i.e., codeine) be restricted to adults 18 years of age and older.

Use of Cough Suppressants

CLINICAL CONNECTION

No patient with a productive cough should be given medication to suppress the cough.

Several principles apply to the use of antitussives, as follows:

- They are helpful and indicated to suppress dry, hacking, non-productive, irritating coughs, especially if the coughing causes sleep loss. A constant nonproductive cough can cause irritation of the trachea, leading to more coughing.
- The cough reflex should not be suppressed in the presence of copious bronchial secretions that need to be cleared. This applies to CF and other chronic obstructive lung diseases, such as chronic bronchitis. Excess mucus secretions from the lower respiratory tract are not present in an uncomplicated cold (see the definition of a common cold at the beginning of the chapter) and indicate the need for further evaluation and possible treatment with an antibiotic.
- The combination of an expectorant and an antitussive in a cold medication is questionable. This combination suppresses the clearance mechanism while also stimulating secretions to be cleared. Use of a single-entity cough preparation to treat a dry, irritating cough is recommended.

Cold Compounds

Table 15.6 lists selected cold remedies, with the classes of agents included in the compounds. Table 15.6 includes single-ingredient products, such as Sudafed, and examples of compounds with multiple drug classes, such as Sudafed PE Sinus and Allergy. Some preparations in elixir form use significant amounts of alcohol as a solvent. NyQuil Cold/Flu liquid contains 10% alcohol; however, alcohol-free products are also available. Another confusing aspect of cold remedies is the variation in ingredients of formulas that are all under the same basic brand name with suffixed initials to indicate substituted or deleted ingredients. For example, Robitussin, Robitussin Cough & Allergy liquid, Robitussin Cold, Cough & Congestion, and Robitussin DAC all vary in ingredients (see Table 15.6). Because these compounds change fairly rapidly, no list remains current in terms of what is on the market. The basic principle of using the typical four classes of combination compounds remains, however, and new compounds can be evaluated for particular uses by considering the effects of these four classes of agents.

Many compounds are available as OTC preparations, thus requiring no prescription. The possibilities of overdose and abuse by combining prescribed compounds and OTC compounds are real. Often OTC preparations have the same classes of ingredients but in lower concentrations.

TABLE 15.6 Categories of Ingredients Found in Selected Cold Medications

Trade Name	Adrenergic	Antihistamine	Expectorant	Antitussive
Claritin 24-Hour Allergy		Loratadine, 10 mg		
Cheratussin AC expectorant cough suppressant			Guaifenesin, 100 mg	Codeine, 10 mg
Mucinex D	Pseudoephedrine, 60 mg		Guaifenesin, 600 mg	
Neo-Synephrine	Phenylephrine, 1%			
Robitussin			Guaifenesin, 100 mg/5 mL	
Robitussin Cough & Allergy liquid	Phenylephrine, 5 mg	Chlorpheniramine, 2 mg		Dextromethorphan, 10 mg
Robitussin DM liquid			Guaifenesin, 100 mg	Dextromethorphan, 10 mg
Sudafed tablets	Pseudoephedrine, 30 and 60 mg			
Sudafed PE Sinus & Allergy tablets	Phenylephrine, 10 mg	Brompheniramine, 4 mg		
Vicks 44 Cough Relief				Dextromethorphan, 10 mg/5 mL
Robitussin Cold, Cough & Congestion	Pseudoephedrine, 30 mg		Guaifenesin, 200 mg	Dextromethorphan, 10 mg
Robitussin DAC	Pseudoephedrine, 30 mg		Guaifenesin, 100 mg	Codeine, 10 mg

Treating a Cold

There is no cure for the common cold, and the four classes of drugs used in cold remedies treat only symptoms. Their potentially undesirable effects, as listed below, should be considered:

- **Sympathomimetics:** Tremor, tachycardia, and increased blood pressure can occur, especially when these agents are used orally. Rebound congestion can occur if used for longer than a day.
- **Antihistamines:** These agents can cause drowsiness and impaired responses. Drying of secretions, whether caused by antimuscarinic or antihistamine action, may suppress a needed defense reaction of the airways. Nocturnal use is indicated more than around-the-clock use.
- **Expectorants:** Many of these agents have questionable efficacy in a cold. The best expectorant, especially with colds, is plain water and juices, avoiding caffeinated beverages, such as tea or colas, and beer or other alcoholic mixtures.
- **Antitussives:** These agents are useful in the presence of an irritating, persistent, nonproductive cough. Productive coughs should not be suppressed, and the rationale behind an expectorant–antitussive combination is questionable.

A combination of all four classes of drugs in one compound does not allow acute or occasional use of the sympathomimetic for decongestion, nocturnal use of antihistamines, and separate use of an expectorant or antitussive, as indicated by symptoms. Single-entity cold medications, such as Sudafed for decongestion or Delsym for cough suppression, are available to treat specific symptoms based on the principles outlined. Fluid intake and rest remain the basic and rational approach to managing colds and preventing spread of the rhinovirus, but this approach is probably the least feasible with the current lifestyles.

RESPIRATORY CARE ASSESSMENT OF COLD AND COUGH AGENTS

Respiratory care assessment of cold and cough agents is directed primarily at cardiac and pulmonary side effects. Many of the agents discussed are OTC preparations, so education of the patient is imperative.

Before Treatment

- Determine whether patient is febrile. If so, this is a distinguishing feature of flu versus common cold.
- Monitor vital signs, including blood pressure, because cold and cough agents can easily affect changes in cardiovascular status.
- Ensure patient is not in need of transportation; some agents may cause drowsiness.
- If selecting a combination agent, determine what is needed to relieve symptoms. Combination agents frequently include agents that are not needed.

During Treatment and Short Term

- Monitor for any changes in vital signs.
- Agents treat only symptoms.

Long Term

- These agents are for short-term use only. Do not overuse or overdose these agents.

General Contraindications

- Decongestant agents can lead to an increase in blood pressure and heart rate. If a patient is being treated for cardiovascular problems, notification of the physician is warranted.
- A productive cough should not be suppressed with an antitussive agent.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Identify the four classes of ingredients found in cold medications.
2. For each of the following agents, identify the category (e.g., adrenergic, antitussive): codeine, chlorpheniramine, phenylephrine, dextromethorphan, pseudoephedrine.
3. What is the intended purpose of α -adrenergic agents in cold medications?
4. What is the intended effect of antihistamines (e.g., histamine 1 [H₁] blockers) in cold medications?
5. Are antihistamines in cold remedies H₁ or H₂ blockers?
6. After you have imbibed several beers at a friend's house after taking a dose of Benadryl, should you drive home? Why, or why not?
7. Identify the most common expectorant in over-the-counter (OTC) cold remedies.
8. Briefly explain how guaifenesin stimulates mucus production.
9. List some specific fluids you would recommend to someone with a cold.
10. Differentiate a "cold" from the "flu."

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 24-year-old respiratory therapy student approaches you after class. His health has been good, he is of normal weight, and he engages in mild but irregular physical activity. He complains of mild malaise, a runny stuffy nose, sneezing, and a slight sore throat. In response to your questions, he denies headache or muscle ache, describes the malaise as very mild fatigue, and states that he has noticed gradually increasing rhinitis over a period of hours, with sneezing beginning during the first 6 hours of these symptoms. He has no fever.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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16

Selected Agents of Pulmonary Value

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CHAPTER OUTLINE

α_1 -Proteinase Inhibitor (Human)

α_1 -Antitrypsin Deficiency

Genetics

Indication for Drug Therapy

Dosage and Administration

Warnings and Adverse Reactions

Respiratory Care Assessment of Therapy of α_1 -Proteinase Inhibitor (Human)

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

Smoking Cessation Drug Therapy

Indication for Use

Drug Formulations

Nicotine Transdermal System

Nicotine Polacrilex (Nicotine Resin Complex)

Bupropion

Varenicline (Chantix)

Precautions

Clonidine (Catapres)

Nortriptyline (Pamelor)

E-Cigarettes

An Alternative or Substitute for Tobacco

Respiratory Care Assessment of Smoking Cessation Drug Therapy

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General Contraindications

Nitric Oxide

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Dosage and Administration

Pharmacology of Nitric Oxide

Effect on Pulmonary Circulation

Toxicity

Contraindications

Respiratory Care Assessment of Nitric Oxide

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Synthetic Analogs of Prostacyclin

Iloprost (Ventavis)

Indication for Use

Dosage and Administration

Precautions

Treprostinil (Tyvaso)

Indication for Use

Dosage and Administration

Precautions

Respiratory Care Assessment of Synthetic Analogs of Prostacyclin

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

Phosphodiesterase 4 Inhibitor

Roflumilast (Daliresp)

Indication for Use

Dosage and Administration

Precautions

Respiratory Care Assessment of Phosphodiesterase 4 Inhibitor

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

Cystic Fibrosis Transmembrane Conductance Regulators

Indication for Use

Dosage and Administration

Precautions

Respiratory Care Assessment of CFTR Agents

Insulin Human (Recombinant DNA Origin)

Insulin Human (Afrezza)

Indication for Use

Dosage and Administration

Precautions

Respiratory Care Assessment of Inhaled Insulin

Before Treatment

During Treatment and Short Term

Long Term

General Contraindications

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms and definitions pertaining to selected agents of pulmonary value
2. Discuss the indication for α_1 -proteinase inhibitor therapy
3. Recognize α_1 -proteinase inhibitor deficiency in a patient
4. List available α_1 -proteinase inhibitors
5. List three types of formulations for nicotine replacement therapy
6. Recognize the advantages and disadvantages of nicotine replacement and medications used for smoking cessation
7. Discuss the use of e-cigarettes as an adjunct or as an alternative to smoking cessation
8. Discuss the indication for nitric oxide
9. Describe the effect of inhaled nitric oxide on a patient
10. List the two toxic products of nitric oxide
11. List the two inhaled prostacyclin analogs available in the United States
12. Name the only inhaled insulin product available in the United States
13. Recognize the need for adding roflumilast to a patient's continuum of care
14. Determine the need for adding Trikafta to a patient's treatment regime

KEY TERMS AND DEFINITIONS

α_1 -antitrypsin (α_1 -AT) Inhibitor of trypsin that may be deficient in patients with emphysema. Also known as α_1 -proteinase inhibitor (α_1 -PI, AT; API).

API deficient Individual has low serum levels of API possessing altered electrophoretic properties.

API dysfunctional Individual has normal serum levels of API, which does not function normally.

API normal Individual has normal serum levels of API, which functions normally.

API null Individual has undetectable serum levels of API.

This chapter presents three groups of drugs that are used for the direct treatment or prevention of respiratory disease: (1) α_1 -proteinase inhibitors (α_1 -PI, APIs), used in the treatment of congenital **α_1 -antitrypsin (α_1 -AT)** deficiency; (2) *nicotine replacement* and other agents used in smoking cessation; and (3) *pulmonary vasodilators*, used for pulmonary hypertension states in newborns and for acute respiratory distress syndrome (ARDS) in adults. Two inhaled *synthetic analogs of prostacyclin* (PGI_2) for the treatment of pulmonary hypertension and inhaled insulin for the treatment of diabetes are described as well.

 α_1 -Proteinase Inhibitor (Human)

KEY POINT

α_1 -Proteinase inhibitor (α_1 -PI, API) is given intravenously to individuals with congenital α_1 -antitrypsin (α_1 -AT) deficiency and who exhibit panacinar emphysema at a young age.

API is also known as α_1 -AT and is intended for the treatment of congenital α_1 -AT deficiency, which leads to emphysema. The product is prepared from pooled human plasma from normal donors, with purification and treatment to remove potentially infectious agents. The disease state is usually termed *α_1 -antitrypsin deficiency*, and the deficient protein is termed *α_1 -proteinase inhibitor*. The terms *α_1 -antitrypsin* and *α_1 -proteinase inhibitor* are used interchangeably, and refer to the same protein.

 α_1 -Antitrypsin Deficiency

α_1 -AT deficiency is a genetic defect that can lead to the development of severe panacinar emphysema. This autosomal recessive

disorder is characterized by serum API levels less than 35% of normal and manifests as panacinar emphysema at age 30 to 50 years. API deficiency is estimated to account for approximately 2% of all cases of emphysema in the United States. It is estimated that there are 60,000 to 100,000 Americans with severe α_1 -AT deficiency.^{1,2} Studies done in the United States vary in their estimates of the prevalence among newborns of α_1 -AT deficiency, ranging from 1 in 2857 to 1 in 5097.³ Among Whites, the genetic disorder α_1 -AT deficiency is as common as cystic fibrosis (CF).⁴ In about 50% of emphysema cases that result from API deficiency there is accompanying chronic bronchitis with mucus hypersecretion, perhaps as a result of secretory cell metaplasia caused by unchecked proteases in the epithelial lining fluid.⁵ Emphysema caused by API deficiency is worse in the lower lung zones and can be markedly accelerated by cigarette smoking.¹

The basic pathology of emphysema resulting from API deficiency is an imbalance between proteases (especially neutrophil elastase [NE]) and antiproteases (especially APIs). The main substrate for API is NE. The pathogenesis of emphysema is described as a process of alveolar wall destruction caused by insufficient protection from the protease NE, an enzyme that can cleave all forms of connective tissue and degrade elastic fiber in the lungs by solubilizing elastin. With inadequate API levels in the lung to balance the protease activity, emphysema occurs at a significantly earlier age than is normally seen. A presentation of severe emphysema at an unexpectedly young age, such as the third or fourth decade, leads to a high suspicion of a genetic defect causing inadequate API levels in blood and subsequently in the lungs. The main role of another protease inhibitor, secretory leukocyte protease inhibitor (sLPI), which is secreted by bronchial glands and goblet cells, is to protect the airway epithelium against proteolytic injury. However, Wewers et al.⁶

provided evidence that API (α_1 -AT) is the predominant antiprotease protecting against NE.

KEY POINT

Individuals who are homozygous (have both recessive alleles) for the defective gene that expresses α_1 -proteinase inhibitor (API) lack this enzyme to balance the action of neutrophil elastase (NE), another enzyme in the lung that solubilizes connective tissue, causing alveolar wall destruction.

Genetics

API is a 54-kilodalton (kDa) glycoprotein encoded by a single gene on chromosome 14. The alleles of the API gene can be categorized as follows⁵:

- **API normal:** Normal serum levels of normal-functioning API
- **API deficient:** Lower than normal serum concentrations of API with altered electrophoretic properties
- **API null:** Undetectable API levels in the serum
- **API dysfunctional:** Normal amounts of abnormally functioning API

Persons with normal alleles for API (designated by the letter *M* for the alleles) are termed *PI*MM*, for protease inhibitor with a pair of the normal alleles. They are homozygous for the normal allele. Normal values for serum API are 150 to 350 mg/dL based on comparison with a commercial standard preparation and 20 to 48 μ M based on comparison with a purified laboratory standard. The commercially available preparations are about 40% higher in concentration than the purified laboratory standards. Results referenced to the commercial standard are expressed as milligrams per deciliter (mg/dL), whereas comparisons with the highly purified (true) standard are given in micromolar units. Commercial standard values can be converted to true standard values by multiplying the commercial value by 0.71.^{5,6}

About 95% of persons in the severely deficient category are homozygous for the *Z* allele and are designated as *PI*ZZ*. Serum levels of API in these individuals range from 2.5 to 7 μ M, or a mean of about 16% of normal.⁵ The *Z* allele is rare in Asians and African Americans. Alleles that do not express API at all are quite rare, and such individuals are designated as *PI type null-null*. *PI type null-null* individuals have an absence of measurable API in serum. Wewers et al.⁶ described the treatment of a patient with the null-null phenotype and no measurable API serum levels. They were able to show that intravenously administered augmentation therapy with α_1 -AT (API) led to normal API levels in blood and in the lung epithelial lining fluid.

The major risk factor for developing emphysema among *PI*ZZ* individuals seems to be cigarette smoking, in which emphysema appears much earlier than in nonsusceptible individuals, as previously noted. Other features seen with airflow obstruction in *PI*ZZ* individuals include a history of pneumonia, episodes of increased cough and sputum production, and a parental history of emphysema.²

CLINICAL CONNECTION

Although replacement therapy is available, traditional medication used to treat chronic obstructive pulmonary disease (COPD) should be continued. Gold COPD Guidelines (goldcopd.org) are useful in the treatment of symptoms.

Indication for Drug Therapy

API therapy is indicated for long-term replacement therapy in individuals with congenital deficiency of API and clinically demonstrable panacinar emphysema. At present, four agents are available; augmentation therapy and maintenance are indicated only for patients who have established API deficiency.⁷ Results from controlled, long-term trials to show that long-term therapy halts the progression of emphysema are unavailable because of inherent difficulties in such trials, including the need for large numbers of patients.¹ API therapy has been provided only to adult subjects. Given the nature of the disease and the action of the drugs, therapy with these drugs cannot reverse damage or improve lung function, and they are extremely expensive, costing \$25,000 to \$40,000 per year of therapy. A cost-effectiveness analysis of Prolastin-C concluded that α_1 -AT replacement therapy is cost effective in individuals who have severe α_1 -AT deficiency and severe chronic obstructive pulmonary disease (COPD).⁸

The American Thoracic Society (ATS) stated that API augmentation therapy should be used for patients with a serum concentration of API less than 11 μ M, or 80 mg/dL.^{2,9} API therapy is not indicated for patients with emphysema related to cigarette smoking who have normal or heterozygous phenotypes.⁵ It is not indicated for individuals with liver disease associated with API deficiency, unless they also have lung disease. ATS guidelines suggest using augmentation therapy if lung function studies become abnormal and if serial studies show deterioration.

Dosage and Administration

The recommended dosage of API is 60 mg/kg of body weight, given once weekly. The dose is given intravenously at a rate of 0.08 mL/kg/min or greater, depending on patient comfort, and usually takes about 15 to 70 minutes for total infusion. Table 16.1 provides a summary of Aralast NP, Prolastin-C, Prolastin-C Liquid, Zemaira, and Glassia.

Warnings and Adverse Reactions

Because API agents are derived from human plasma, there is a risk of disease transmission. Although there was some variation in reactions to each API agent, fever, exacerbation, and flu-like symptoms were most common.

TABLE 16.1 α_1 -Proteinase Inhibitors Currently Available

Brand Name	Strength (mg)
Aralast NP*	500 and 1000
Glassia†	1000‡
Prolastin-C*	500, 1000, and 4000
Prolastin-C Liquid†	
Zemaira*	1000, 4000, and 5000‡

*Powder form; reconstitution must take place before administration.

†Ready to use liquid; no reconstitution needed.

‡Must be administered through a 5-micron filter.

RESPIRATORY CARE ASSESSMENT OF THERAPY OF α_1 -PROTEINASE INHIBITOR (HUMAN)

Respiratory care assessment of α_1 -AT replacement therapy is directed primarily at lung function and the rate of change of airflow obstruction in patients.

Before Treatment

- Pulmonary function testing of flow rates is used to monitor the degree of airflow obstruction over long-term use of the drug.

During Treatment and Short Term

- Smoking status should be monitored, and individuals with α_1 -AT deficiency who smoke should receive both education on the effect of smoking with this disease and direction to resources to aid in smoking cessation (drug therapy and behavior modification assistance).

Long Term

- Overall pulmonary health should be assessed based on the frequency and severity of respiratory infections; cough; sputum production, if present; and hospitalization rate.

General Contraindications

- API agents are derived from human plasma; therefore disease transmission is possible.

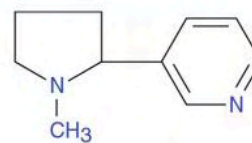
Smoking Cessation Drug Therapy

KEY POINT

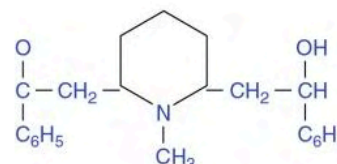
Smoking cessation agents include nicotine-containing transdermal patches, chewing gum, nasal spray, and inhaler as a substitute therapy for smoking cessation in individuals with a strong physical addiction and who suffer from withdrawal symptoms from nicotine absorbed during smoking. A tapered dose regimen allows for withdrawal with minimal symptoms and assists in reducing the craving for cigarettes. Bupropion, an antidepressant, varenicline, a benzazepine derivative, and cytisine, a plant-based alkaloid that, like varenicline, is a selective partial agonist at nicotinic acetylcholine receptors, are known to be helpful in smoking cessation. In 2019, e-cigarette use in young adults, aged 18–24 years, was at 9.3%, which is higher than any other adult age group. These odds are not promising because, in 2020, one in five (20%) high school students had used e-cigarettes, many of whom were not smokers in the first place. Their use as a smoking cessation tool is still under review.

Nicotine and lobeline are naturally occurring alkaloids that are capable of stimulating acetylcholine receptors at the autonomic ganglia of the sympathetic and the parasympathetic systems and cholinergic nicotinic receptors at skeletal muscle sites (see [Chapter 5](#)) and in the brain. The diagramed structures of these two agents are shown in [Fig. 16.1](#). The affinity of nicotine for ganglionic and neuromuscular receptor sites led to the use of the term *nicotinic* to distinguish these receptors from *muscarinic* receptors because these receptors use acetylcholine as a neurotransmitter.

Lobeline is a plant derivative that has less potency than nicotine but a similar spectrum of action. Nicotine itself has a greater affinity for ganglionic receptors than for skeletal muscle nicotinic



Nicotine



Lobeline

• **Fig. 16.1** Chemical structures of nicotine and lobeline, both of which are nicotinic agonists.

receptors. The response to nicotine stimulation involves the simultaneous discharge of the sympathetic and parasympathetic systems. The sympathetic effect predominates in the cardiovascular system, with hypertension, tachycardia, and peripheral vasoconstriction. Part of the sympathomimetic effect is mediated by nicotinic stimulation of receptors on the adrenal medulla, leading to the release of epinephrine and norepinephrine. Nicotine produces a parasympathetic effect in the gastrointestinal and urinary tracts, with nausea, vomiting, diarrhea, and urination. Response to nicotine is dose dependent, and increasing or toxic doses can produce a depolarizing blockade of receptors. Stimulation of neuromuscular receptors causes tremor and loss of steadiness of hands.

In addition to stimulating nicotinic receptors at the autonomic ganglia, neuromuscular junctions, and adrenal medulla, nicotine binds to receptors in the central nervous system (CNS). This action causes respiratory stimulation, tremors, convulsions, nausea, and emesis. The last two effects are common when nicotine is first inhaled as tobacco smoke, although tolerance develops rapidly. Nicotine is the chief alkaloid in tobacco products, and nicotine addiction is the basis for tobacco dependence. In a seasoned smoker, within seconds of inhaling from a cigarette, the internal carotid arteries carry a large bolus of nicotine to the brain, where the nicotine binds to nicotinic receptors.¹⁰ This binding causes secretion of dopamine, which causes a feeling of pleasure and cognitive arousal. Nicotine also increases levels of norepinephrine, β -endorphin, acetylcholine, serotonin, and other substances in the CNS, all of which increase the sensation of euphoria and well-being; enhances concentration, alertness, and memory; and decreases tension and anxiety. Sensitivity and responsiveness to nicotine in the CNS are genetically determined and constitute the basis for forming the physiologic addiction to nicotine. Without the proper genetic substrate, a smoker cannot become nicotine dependent. About 10% of smokers lack this substrate and are not physiologically dependent; 90% have the substrate and are addicted to nicotine to varying degrees.¹⁰

Cigarette smoking among US adults (aged ≥ 18 years) declined from 20.9% in 2005 to 15.5% in 2016. Yet, nearly 38 million American adults smoked cigarettes in 2016.¹¹ Smoking cessation is the most effective measure to decrease the rate of forced expiratory volume in 1 second (FEV₁) decline.¹² Withdrawal from nicotine in tobacco products is difficult because the stimulatory and

reward effects are lost, resulting in physical symptoms, including craving for nicotine, nervousness, irritability, anxiety, drowsiness, sleep disturbance, impaired concentration, and increased appetite with attendant weight gain. Nicotine replacement therapy (NRT), in various dosing formulations, is intended to aid in smoking cessation by allowing initial replacement and then gradual withdrawal of the nicotine found in tobacco. Because nicotine is well absorbed from the skin and mucosa, various forms of evidence-based NRT—transdermal patch, chewable gum formulation, nasal spray, and inhaler—are available to aid in smoking cessation.

Indication for Use

Nicotine replacement agents relieve nicotine withdrawal symptoms. NRT should be used as part of a comprehensive smoking cessation program to increase compliance and prevent relapse. Smokers with signs of strong physical dependence on nicotine may benefit the most from NRT. Signs of strong physical dependence¹⁰ are listed in [Box 16.1](#).

• BOX 16.1 Signs of Strong Physical Addiction or Dependence on Nicotine

- Smokes more than 15 cigarettes per day
- Prefers brands with nicotine levels above 0.9 mg
- Has habit of inhaling smoke frequently and deeply
- Smokes within 30 minutes of rising
- Finds it difficult to give up the first morning cigarette and smokes more frequently in the morning
- Finds it difficult to refrain from smoking in smoke-free environments
- Smokes even when ill enough to be bedridden

CLINICAL CONNECTION

Any therapy to reduce the use of tobacco must include counseling. A comprehensive smoking cessation program includes an interdisciplinary team of health care providers.

Drug Formulations

Cessation drug therapy includes various formulations of agents. The US Department of Health and Human Services Public Health Service 2008 update on the guidelines to treat tobacco dependence categorizes pharmacotherapy into first-line and second-line agents.¹³ First-line medications include nicotine replacement, bupropion, and varenicline (Chantix). Cytosine is licensed for use in some eastern and central European, and central Asian countries and was recently approved as a natural health product in Canada, but it is not currently approved by the US Food and Drug Administration (FDA) for smoking cessation. Second-line agents include clonidine (Catapres) and nortriptyline (Pamelor). [Table 16.2](#) lists pharmaceutical details on the various agents in use at the time of this writing. Details on nicotine substitute agents can be found in the manufacturers' literature.¹⁴

Nicotine Transdermal System

A nicotine transdermal system is a multilayered unit that delivers time-released nicotine for 24 hours after application to the skin. Approximately 68% of the nicotine released from the system enters the circulation. Products may differ in their kinetics based on diet, age, sex, certain diseases and medications, and smoking itself. These latex-free transdermal products provide a more consistent level of nicotine compared with the gum or the lozenge. This is an easy, convenient, and inconspicuous method of nicotine

TABLE 16.2 Smoking Cessation Drug Formulations

Category	Brand Name	Dosage
Nicotine transdermal system	NicoDerm CQ (OTC*) 21 mg/day for first 6 wk, 14 mg/day for next 2 wk, 7 mg/day for last 2 wk	
Nicotine polacrilex (Nicotine Resin Complex)	Nicorette (gum)	2 mg if <25 cigarettes/day: 9 pieces/day, maximum 24 pieces/day; 4 mg if ≥25 cigarettes/day: 9 pieces/day, maximum of 24 pieces/day
	Nicorette (lozenge)	2 mg and 4 mg, no more than 5 lozenges in 6 hr, maximum 20 lozenges/day
	Nicotrol NS	0.5 mg/spray, one in each nostril (1 mg); 1 or 2 doses/hr (2 sprays with nasal spray, 1 each nostril, is 1 dose), up to 5 doses/hr, or 40 doses/day
	Nicotrol Inhaler	4 mg/use; recommended dosage 24–64 mg (6–16 cartridges)/day, up to 12 wk, with gradual reduction over 12 wk
Nonnicotine—antidepressant	(Generic-Bupropion)	150-mg sustained-release tablets; begin at 150 mg/day for 3 days; increase to 150 mg/day bid, with maximum of 300 mg/day, interval of 8 hr between doses; continue treatment for 7–12 wk
	Pamelor (Generic-Nortriptyline)	25-mg tablet daily, increasing to 100 mg daily
Nonnicotine—nicotinic receptor agonist	Chantix (Generic-Varenicline)	1-wk titration of 0.5 mg once daily for first 3 days, twice daily for remainder of week; begin 1 mg twice daily for 11 wk
Nonnicotine—antihypertensive agent	Catapres (Generic-Clonidine)	0.10-mg tablet daily, increasing by 0.10 mg as needed; 0.10-mg transdermal patch daily, increasing to 0.20-mg patch as needed

*Committed quitters.
OTC, Over the counter.

replacement delivery. A common side effect is skin irritation at the site, but this is minimized by alternating the sites of application. Any skin site that is clean, dry, and hairless can be used. The largest patch (21 mg) is equal to approximately half a pack of cigarettes per day. Compliance with recommended nicotine replacement transdermal plans leads to higher rates of cessation compared with nicotine polacrilex over-the-counter (OTC) products.¹⁵

Nicotine Polacrilex (Nicotine Resin Complex)

Nicotine polacrilex, a resin complex, is available as a piece of chewing gum, lozenge, nasal spray, or inhaler. *Nicotine polacrilex gum* contains nicotine bound to an ion-exchange resin in a chewing gum base. The gum can be difficult to chew, causing jaw ache, and has a bad taste. Absorption of the active nicotine can be inconsistent, although it is faster than with the transdermal patch. Absorption of nicotine is reduced if acidic beverages, such as coffee, soda, or orange juice, are taken simultaneously. Users are instructed to chew the gum until it becomes malleable, then “park” it between the cheek and the gums, repeating this every few minutes or each time the taste is gone. Chewing slowly titrates the dose of nicotine received. Intermittent, rather than continuous, chewing slows the buccal absorption of the nicotine released; this also slows the amount of nicotine swallowed, which is not well absorbed from the stomach and can cause gastrointestinal irritation. Each piece of gum (2 or 4 mg) delivers about 50% of its nicotine.

The *nicotine lozenge* is a hard resin complex that is bound with nicotine. The lozenge is placed in the user’s mouth to dissolve slowly, with occasional transfer from side to side until dissolved. Users should refrain from drinking liquids 15 minutes before or during use and should not chew or swallow the lozenge.

The *nicotine nasal spray* offers the advantage of producing rapid peak plasma levels of nicotine by delivering the spray directly to the nasal membranes, which may help to reduce or control cravings for a cigarette. Irritant effects with the nasal spray may include runny nose and nasal irritation, sneezing, cough, and watery eyes. Although rapid relief may be obtained, administration is more meddlesome than with the patch or the gum formulations.

The *nicotine inhaler* offers smokers a “simulated cigarette”; the kit contains a 10-mg/cartridge unit dose, which delivers 4 mg/use; a mouthpiece; blister trays of nicotine cartridges; and a plastic case. The use of a mouthpiece resembling a cigarette holder allows for delivery of the nicotine like smoking a cigarette, with oral gratification. This system delivers less nicotine than the other systems. All of the nicotine is absorbed across the oropharyngeal membranes.¹⁰ The inhaler may be most useful in a smoker with low dependency, as an adjunct to the patch to treat sudden cravings, or in combination with bupropion.

Bupropion

Bupropion is an antidepressant once known as Zyban and can be found in Wellbutrin SR and Wellbutrin XL; it is also a non-nicotine aid to smoking cessation. The drug is a relatively weak inhibitor of neuronal uptake of norepinephrine, serotonin, and dopamine, which is the basis for its antidepressant effect. The exact mechanism by which bupropion aids in smoking cessation is unknown. Bupropion may relieve nicotine withdrawal by slowing the normal reuptake of dopamine or preventing its breakdown in the CNS. Bupropion is effective even if the smoker is not depressed because mood and emotional state are related to the need for smoking and craving for nicotine.¹⁰ Furthermore, symptoms of nicotine dependence among smokers are correlated

with the magnitude of symptoms of depression. Subjects who are depressed are less likely to be able to quit smoking. This finding would indicate that the antidepressant effect of bupropion assists in smoking cessation. Jorenby et al.¹⁶ found that only about 6% of smokers succeed in quitting with no NRT.¹⁶ However, when bupropion and the nicotine patch are used in combination, the cessation rate is 35.5%. This study suggests that bupropion added with nicotine substitutes in a program of smoking cessation is helpful.

The use of bupropion is associated with a dose-dependent risk of seizure. Doses less than 300 mg/day are generally safer and have a risk of about 0.1% for seizure. If a patient has not made significant progress toward abstinence from smoking by week 7, it is unlikely that the effort will be successful, and bupropion should be discontinued. Dose tapering for discontinuation is not required.

Administration of bupropion with a monoamine oxidase inhibitor (MAOI) or other medications containing bupropion is contraindicated. The drug should not be used by individuals with seizure disorders or those with bulimia or anorexia nervosa because both these conditions have a higher incidence of seizures.

Varenicline (Chantix)

Varenicline is a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist developed for explicit use in smoking cessation. Varenicline (Chantix) works by attaching to $\alpha_4\beta_2$ receptors, inhibiting the activation of this receptor by nicotine. The sensation produced by smoking is blocked and prevents the cycle of nicotine addiction.¹⁷ Varenicline is administered in a 12-week-long treatment process that begins with a 1-week titration process. The most common adverse reactions from the use of varenicline were nausea, insomnia, constipation, and vomiting.

In clinical trials, varenicline produced a 39% quit rate compared with 20% for bupropion and 11% for placebo after 12 weeks.¹⁸ In another study, varenicline produced quit rates of 44% and 49%, respectively, at lower and higher doses of the drug compared with placebo (12%).¹⁹ Ebbert et al.²⁰ found that participants taking a combination of varenicline and bupropion SR at 52 weeks achieved a 31% prolonged abstinence rate in a randomized multicenter controlled trial. Anthenelli et al.,²¹ in a double-blind, randomized, placebo-controlled clinical trial, found that varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patches were more effective than placebo. However, a 2017 study by Leas et al. found no evidence that pharmaceutical cessation aids improved the chances of quitting smoking in the long term.²² It may be that previous studies included intensive behavioral counseling, which may explain these differences.

Precautions

Individuals receiving NRT should be informed that the replacement formulations do contain active nicotine. If nicotine replacement products are used while still using tobacco products, potentially toxic concentrations of nicotine in the blood can occur. Transference of nicotine dependency from the tobacco product to the replacement product can occur. Use within a program of smoking cessation is encouraged to achieve complete withdrawal. Replacement formulations should be gradually withdrawn and stopped by 3 months. Careful consideration should be given to the use of NRT in patients with cardiovascular disease, including

coronary artery disease, cardiac arrhythmias, or vasospastic disease, and in patients with hypertension.

Health care workers should avoid handling active nicotine products such as patches because nicotine is easily absorbed through the skin. Used products must be disposed of properly so that children or pets are not exposed.

Clonidine (Catapres)

Clonidine (Catapres) is an antihypertensive agent that has been prescribed to reduce symptoms of opioid and alcohol withdrawal.¹³ At present clonidine is not approved by the US FDA for use as a smoking cessation aid. It can be taken orally or is available as a transdermal patch. Common side effects include drowsiness, fatigue, depression, nausea, and weight gain. More importantly, this agent should not be stopped abruptly; this can cause nervousness, tremors, headache, and increased blood pressure.

Nortriptyline (Pamelor)

Nortriptyline is a tricyclic antidepressant approved by the FDA to treat depression. It is not FDA approved for use as a smoking cessation aid. However, similar to bupropion, it is thought to affect tobacco dependence because of its antidepressant mode of action. As with other antidepressants, common side effects include dizziness, insomnia, and blurred vision.

E-Cigarettes

Electronic cigarettes, or e-cigarettes, were introduced in the early 2000s. The inventor, a Chinese pharmacist and smoker, reportedly created the device for his father, who was a heavy smoker and died as a result of lung cancer. In 2006, e-cigarettes were introduced in Europe and the United States.²³ Currently, there are concerns about the safety of e-cigarette use because of the lithium batteries catching fire and, more importantly, the normalization of smoking behavior, especially among teenagers and young adults.²⁴ A recent article by Abrams et al.²⁵ advocates for the use of e-cigarettes as a “harm minimization” strategy for traditional smokers. The reason postulated is that smoking-related diseases are not caused by nicotine but by the lethal mix of carbon monoxide and the more than 70 known toxins found in cigarettes. Abrams et al. further stated that e-cigarettes provide a means for competition and even replacement of traditional cigarette use. However, other evidence is becoming available that e-cigarettes have harmful metals,²⁶ contain benzaldehyde when food flavoring solutions are added, especially cherry-flavored products,²⁷ and contain between 0 and 30 mg/mL of nicotine.²⁸

As a strategy for smoking cessation, e-cigarettes are continually changing and presently there is not enough evidence to conclude that e-cigarettes, in general, increase smoking cessation. Moreover, the available evidence indicates that a majority of e-cigarette users also smoke conventional cigarettes—a pattern of use that does not confer a substantial risk reduction benefit to the individual.²⁹

An Alternative or Substitute for Tobacco

E-cigarettes and e-cigarette products were authorized by the FDA in October 2021 to stay on the market. One advantage of the e-cigarette delivery system is that nicotine serum concentrations peak within 5 minutes, and this mimics the traditional cigarette. NRT has a much slower nicotine absorption rate through the skin or the buccal mucosa and is therefore not effective as an

immediate alternative.³⁰ Whether e-cigarettes are a safer option for traditional cigarette smokers, however, is still being debated. Most adult e-cigarette users are current or former smokers.²⁹ Evidence now indicates that most new users of e-cigarettes are adolescents who are in middle school or high school.³¹ Some believe that e-cigarettes are a gateway to cigarettes and nicotine addiction in high school adolescents because e-cigarettes tend to normalize smoking behavior.³² Finally, the practice of adding homemade solutions and cannabis oil to liquid tanks of e-cigarettes is a cause for concern. Besides the unknown long-term effects of this new practice, as well as the legal and medical issues, it is concerning that adolescents are experimenting with e-cigarettes during a time of critical brain development. Fortunately, the number of scientific studies on e-cigarettes and smoking cessation among adults are increasing. A growing body of scientific evidence suggests that multiple factors related to e-cigarettes, including product type, frequency of use, and efficiency of nicotine delivery, could affect the efficacy of these products for successful smoking cessation. Lastly, the diversification of the e-cigarette market is important to consider in the context of cessation efficacy, as various aspects of these products, including their ability to efficiently deliver nicotine to the user, have evolved with each generation of e-cigarette product that has entered the marketplace.³³

It is important to note that the American Cancer Society and the American Heart Association have issued position statements that e-cigarettes may help smokers to quit using tobacco and that using the current generation of e-cigarettes is less harmful than smoking cigarettes. Both organizations also acknowledge that e-cigarettes may encourage teens to smoke and that the health effects of the long-term use of e-cigarettes are not known.^{34,35}

RESPIRATORY CARE ASSESSMENT OF SMOKING CESSATION DRUG THERAPY

The primary outcome of interest with smoking cessation drug therapy is success in quitting for the long term.

Before Treatment

- A patient must be willing to quit. The higher the willingness, the more successful will be the outcome.

During Treatment and Short Term

- Monitor abstinence rates at intervals of 3, 6, or 12 months.
- Monitor for symptoms of nicotine overdosing (possible if subjects continue smoking while using nicotine substitutes), such as nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, disturbed vision and hearing, mental confusion, or marked weakness.
- Assess bupropion use for improvement in emotional attitude, including a reduction in irritability, anxiety, difficulty in concentrating, or depression.
- Assess varenicline use for improvement in nicotine withdrawal symptoms.
- Assess clonidine and nortriptyline for possible use as smoking cessation aids.
- Monitor clonidine for adverse actions related to cardiovascular status.
- Monitor nortriptyline for change in an emotional state.
- Assess the use of e-cigarettes to help reduce tobacco use.

Long Term

- Assess patients for weight gain, and encourage an exercise program to prevent relapse caused by a desire for appetite control.
- Continue to provide counseling and support throughout treatment for smoking cessation.

General Contraindications

- Nicotine replacement agents contain nicotine. Continue monitoring for nicotine overdosing.
- Smoking with concurrent use of nicotine replacement agents should be discouraged.
- E-cigarettes may be a gateway to tobacco use.
- Mental status with the use of nonnicotine agents should be evaluated.

Nitric Oxide

KEY POINT

Nitric oxide (NO) is approved for pulmonary vascular relaxation and is used in the treatment of persistent pulmonary hypertension in newborns.

Nitric oxide (NO) is a product of endothelial cells that acts as a nitrovasodilator. It was investigated for its ability to reduce pulmonary vascular resistance in various disease states, such as persistent pulmonary hypertension of the newborn (PPHN) and ARDS. Furchgott and Zawadzki³⁶ showed that the endothelial cells in blood vessels elaborate a short-lived vasodilator, which was termed *endothelium-derived relaxing factor (EDRF)*. The neurotransmitter acetylcholine, which can normally dilate blood vessels, has no effect or vasoconstricts if applied to blood vessels without endothelium. Subsequently, the substance EDRF was identified by Palmer et al.³⁷ and Ignarro et al.³⁸ as NO. This endogenously produced vasodilator, as a gas, can be inhaled, and this can cause pulmonary vasodilation.³⁷

Indication for Use

NO is approved for use in neonates with hypoxic respiratory failure to reduce pulmonary artery pressure and to increase oxygenation in newborns with pulmonary hypertension and hypoxia. Off-label use of NO in adults with ARDS has been reported; however, data on its effectiveness are conflicting and it has not been reported useful in reducing mortality in ARDS.³⁹

NO (INOMax, Noxivent, and GENOSYL) is used in conjunction with ventilatory support and other critical care measures in the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. Off-label uses of NO include reduction of pulmonary vascular resistance and pulmonary artery pressure during neonatal cardiac surgery, treatment of hypoxemia or pulmonary hypertension after lung transplantation, and treatment of ARDS.⁴⁰ NO has been approved with an orphan drug designation.

CLINICAL CONNECTION

A right-to-left shunt allows blood to flow from the right side of the heart to the left. The most common right-to-left shunt in a newborn is called *tetralogy of Fallot*. Nitric oxide (NO) therapy should *not* be used in patients who are dependent on a right-to-left shunt.

Dosage and Administration

NO gas is available in a concentration of 800 parts per million (ppm). The recommended dose is 20 ppm. The treatment should be maintained up to 14 days or until the underlying oxygenation problem has been resolved and the neonate can be successfully weaned from NO. In the Neonatal Inhaled Nitric Oxide Study (NINOS) trial, most patients failed to improve on 20 ppm and the dose was increased to 80 ppm, but no response occurred at the higher concentration.⁴¹ The risk of methemoglobinemia and elevated nitrogen dioxide (NO₂) levels increases significantly at doses greater than 20 ppm, as discussed subsequently. Doses greater than 20 ppm are not recommended.

The safety and effectiveness of NO were established in patients with hypoxic respiratory failure receiving other critical care support, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Additional therapies might be needed to maximize oxygen delivery, such as surfactant administration and high-frequency oscillatory ventilation. Information about the effectiveness of NO therapy in infants older than 14 days of age or in adults is unavailable.

The use of NO in preterm infants and very young infants has not received FDA approval. However, according to Kinsella et al.,⁴² the Pediatric Pulmonary Hypertension guidelines recommend the following for premature infants:

- NO therapy should not be used prevent bronchopulmonary dysplasia (BPD).
- NO therapy is advantageous in preterm infants with PPHN who have severe hypoxemia.
- NO therapy is the preferred pulmonary vasodilator for use in preterm infants.

A summary of the guidelines for the safe administration of NO, based on several sources listed in the references, including a statement by the American Academy of Pediatrics, is as follows^{39,43}:

- Blending and delivery systems should be designed and tested for accurate NO delivery, minimum NO₂ production, and capability of administering NO in constant concentration ranges in parts per million or less throughout the respiratory cycle.
- The delivery system should be calibrated by using a precisely defined mixture of NO and NO₂.
- Sample gas for analysis should be drawn before the Y-piece, proximal to the patient.
- Inhaled NO and NO₂ should be monitored continuously, using chemiluminescence or electrochemical analyzers.
- Oxygen levels in the inspired gas should be measured.
- Blood methemoglobin levels should be measured frequently.
- The minimal effective concentration of NO should be used.
- Weaning from NO should be gradual to prevent arterial desaturation and pulmonary hypertension.
- Because inhaled NO is used in respiratory failure, institutions that offer NO therapy generally should have extracorporeal membrane oxygenation (ECMO) capability in the event NO therapy fails. Alternatively, a plan for timely transfer of infants to a collaborating ECMO center should be established prospectively, and transfer should be accomplished without interruption of NO therapy.

In the clinical use of NO to manage pulmonary hypertension, the following has particular significance: when withdrawing NO, rebound hypertension occurs; this can be severe and cause oxygen desaturation. Rebound pulmonary hypertension may be caused by a downregulating effect on endogenous NO production in the pulmonary endothelium. The vasodilating effect of inhaled NO

ends with the removal of the gas because of its short half-life (as subsequently described), which is a result of its binding to hemoglobin. An increase in the fractional concentration of oxygen in inspired gas (FiO_2) up to 1.0 may be needed as the inhaled NO is terminated. FiO_2 can be reduced over the next few hours as pulmonary hemodynamics restabilize. Close monitoring of arterial oxygenation is crucial when weaning from NO.

KEY POINT

Nitric oxide (NO) is administered as an inhaled gas; it readily diffuses into the vascular endothelium, where it stimulates guanylyl cyclase in the cell, increases cyclic guanosine monophosphate (cGMP), and produces smooth muscle relaxation. NO also quickly diffuses into the bloodstream, where it is inactivated by binding to hemoglobin, producing methemoglobin. NO has a short half-life of less than 5 seconds because it is quickly bound by hemoglobin. In the presence of oxygen, NO is converted to nitrogen dioxide, a nitrite toxic to the lung.

Pharmacology of Nitric Oxide

The formation, mode of action, and fate of endogenous NO are diagrammed in Fig. 16.2. NO is formed endogenously in the vascular endothelial cells of the respiratory tract from the precursor amino acid L-arginine by several isoforms of the enzyme nitric oxide synthase (NOS). NOS requires the cosubstrates nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen (O_2). In the reaction, nitrogen is contributed by the arginine; O_2 , by the oxygen molecule; and a free electron, by NADPH. NOS is categorized as constitutive NOS (cNOS), including that found in endothelial cells (eNOS) and in neurons (nNOS), and as inducible NOS (iNOS).³⁵ The vascular relaxation caused by acetylcholine is due to stimulation of cNOS, which results in an increase in NO. Histamine, leukotrienes, and bradykinin are other mediators that increase cNOS-mediated NO and promote vasodilation and lowering of blood pressure.

Proinflammatory cytokines, such as interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-1 (IL-1), can induce iNOS to increase endogenous levels of NO. Glucocorticoids block the induction of iNOS and inhibit the formation of NO.³⁶ NO is the active form of nitrovasodilators, such as

nitroglycerin and sodium nitroprusside.³⁸ NO has also been identified as at least one of the neurotransmitters in the nonadrenergic, noncholinergic (NANC) inhibitory nervous system³⁷ (see Chapter 5). The endogenous production of NO can be inhibited by L-arginine analogs, which inhibit NOS—for example, *N*-nitro-L-arginine. The NO molecule is small and lipophilic, and it has a very short duration of action of 0.1 to 5 seconds in physiologic systems.³⁶

NO is generated in vascular endothelial cells and diffuses rapidly into myocytes in the endothelium, binding to guanylyl cyclase. Guanylyl cyclase (also termed *guanylate cyclase*) stimulates the production of cyclic guanosine-3',5'-monophosphate (cGMP), which causes a decrease in intracellular calcium and consequent vascular or nonvascular smooth muscle relaxation. The NO-induced increase in cGMP within the cells also inhibits platelet adherence and aggregation and polymorphonuclear leukocyte chemotaxis.⁴³ NO readily diffuses into the blood vessel itself and into endothelial cells and enters red blood cells (RBCs) to bind rapidly with hemoglobin, forming methemoglobin and becoming inactivated in the process. NO is also converted in RBCs to nitrate, and some endogenous NO is exhaled from the lung. Because NO diffuses so readily into the bloodstream and is inactivated by being bound to hemoglobin, its action is limited to the pulmonary vascular endothelium, whether generated endogenously within the lung or inhaled as an exogenous gas. It is a selective pulmonary vasodilator. The end products of NO that enter the systemic circulation are predominantly methemoglobin and nitrate. Nitrite is the predominant NO metabolite excreted in urine, accounting for greater than 70% of the inhaled dose.

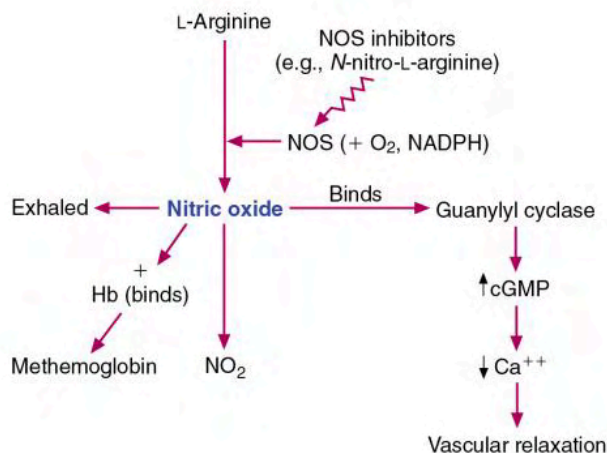
Effect on Pulmonary Circulation

With normal pulmonary hemodynamics (normal vascular resistance), inhalation of NO produces no effect on pulmonary arterial pressure or gas exchange.³⁶ However, Frostell et al.⁴⁴ reported that hypoxic pulmonary vasoconstriction caused by breathing 12% oxygen in healthy adults increased mean pulmonary arterial pressure from 14.7 ± 0.8 mm Hg to 19.8 ± 0.9 mm Hg. This increase in pulmonary arterial pressure was reversed by adding 40 ppm of NO to the gas mixture. No change occurred in systemic vascular resistance because NO was inactivated locally by hemoglobin. Taylor et al.⁴⁵ found that 5 ppm of NO successfully improved oxygenation in the short term for patients with acute lung injury.

Toxicity

Toxicity with exposure to NO can be caused by the NO itself, by the formation of the nitrite, NO_2 , and the formation of methemoglobin. NO can be a mediator of lung injury, for example with paraquat poisoning, in which inhibition of nitric oxide synthase reduces the amount of lung injury. NO_2 is a strong oxidizer that causes lipid peroxidation in cells. The amount of NO_2 produced depends on the amount of NO and the amount of surrounding O_2 . The higher the FiO_2 , the greater the amount of oxidation of NO to NO_2 . Similarly, the higher the concentration of NO, the shorter the time to achieve oxidation to NO_2 . The lethal effect of NO_2 results from pulmonary edema, and short-term exposure to greater than 150 ppm of NO_2 is usually fatal. In the usual doses of NO, such as 0.5% to 4%, methemoglobinemia is not usually a problem, although this should be monitored.

It is unknown whether NO can cause fetal harm when given to pregnant women, and the manufacturer notes that it



• **Fig. 16.2** Production, physiologic effect, and metabolism of endogenous nitric oxide. cGMP, Cyclic guanosine 3',5'-monophosphate; Hb, hemoglobin; NADPH, nicotinamide adenine dinucleotide phosphate; NO_2 , nitrogen dioxide; NOS, nitric oxide synthase.

is not intended for use in adults. It is unknown whether NO is excreted in human milk. Occupational exposure to NO is set by the Occupational Safety and Health Administration (OSHA) at 25 ppm, and exposure to NO₂ is set at 5 ppm (manufacturer's literature).

Contraindications

NO should not be used in neonates who are known to be dependent on right-to-left shunt.

RESPIRATORY CARE ASSESSMENT OF NITRIC OXIDE

Before Treatment

- Because NO is administered in conjunction with ventilatory support, the usual measures of critical care assessment and in particular ventilator monitoring should be followed.

During Treatment and Short Term

- Evaluate therapy for a reduction in the oxygenation index (OI = mean airway pressure in cm H₂O × FiO₂/PaO₂).
- Evaluate the effect of NO and monitor the partial pressure of arterial oxygen (PaO₂) and the overall level of ventilatory support (FiO₂, inspiratory pressure and time, end-expiratory pressure, rate).
- Monitor preductal and postductal pulse oximetry (saturation of peripheral capillary oxygen [SpO₂]) to evaluate shunting.
- If available, review echocardiogram to evaluate right-to-left shunting.
- Monitor inspired NO and NO₂, along with methemoglobin.
- Monitor cardiovascular status and stability, including the level of intravenous fluids and vasoactive medications needed.

Long Term

- Continue assessment of O₂, NO, NO₂, and methemoglobin levels.

General Contraindications

- NO should not be used in neonates who are dependent on a right-to-left-shunt.

Synthetic Analogs of Prostacyclin

At present, two inhaled forms of synthetic prostacyclins (PGI₂s) are FDA approved to help alleviate shortness of breath in individuals with pulmonary hypertension. The two agents available in the United States are iloprost (Ventavis) and treprostinil (Tyvaso). However, epoprostenil sodium (Flolan) as an inhalation agent has been prescribed for off-label use in adults and children.

Iloprost (Ventavis)

KEY POINT

Iloprost is an inhaled prostacyclin (PGI₂) available in the United States.

Iloprost is a synthetic analog of PGI₂. The drug Ventavis is made available as an inhalation solution that is delivered via the I-neb AAD (adaptive aerosol delivery) system. Ventavis dilates systemic and pulmonary arterial vascular beds.

Indication for Use

Ventavis is indicated for the treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) class III or IV symptoms. NYHA is a functional and therapeutic classification of physical activity in patients with cardiac dysfunction. The classification, I through IV, describes the limitations of physical activity; NYHA III and IV are higher and pose considerable restriction on patient activity. Ventavis is not intended for pediatric use; it is intended for adults 18 years of age and older. In clinical studies, Ventavis has been shown to improve NYHA functional class, improve exercise capacity, and increase walking distance.⁴⁶

Dosage and Administration

Ventavis is supplied in 1-mL ampules with two concentrations available—10 and 20 mcg/mL. An initial dose of 2.5 mcg should be administered and evaluated for tolerability. If tolerated, increasing the dose to 5 mcg is acceptable. Ventavis should be administered six to nine times daily during waking hours. Doses should be given more than 2 hours apart. Ventavis is an inhalation solution. This agent should be nebulized only with the intended aerosol devices.

Precautions

Ventavis has not been studied in patients with underlying lung disease (e.g., asthma, COPD). Ventavis can cause bronchospasm. It should not be mixed with any other agents; however, patients with underlying lung disorders may benefit from pretreatment with a β agonist.

Treprostinil (Tyvaso)

KEY POINT

Tyvaso is an inhaled prostacyclin (PGI₂) vasodilator used for the treatment of pulmonary hypertension.

Treprostinil was first approved by the FDA as an injectable form in 2002. Since that time, research has been ongoing to create and test an inhaled version.⁴⁷ Inhaled treprostinil (Tyvaso) was approved for use in the United States in 2009. Tyvaso is a PGI₂ analog that causes vasodilation of the pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. It is administered using the Tyvaso Inhalation System (United Therapeutics Corp., Silver Spring, Maryland), which is an ultrasonic, pulsed-delivery device. Tyvaso DPI is now available in a dry powder. The DPI is the same device (MannKind Corp.) used with Afrezza.

Indication for Use

Tyvaso is indicated for the treatment of pulmonary arterial hypertension to increase walking distance in patients with NYHA class III symptoms. Tyvaso is not intended for use in patients younger than 18 years of age.

Dosage and Administration

Tyvaso is available in a 2.9-mL ampule, which contains 1.74 mg of treprostinil (0.6 mg/mL). It is nebulized in the Tyvaso Inhalation System. The ampule is dumped into the medication cup of the nebulizer and is used for the entire day.

The patient nebulizes the prescribed amount of drug in four separate, equally spaced treatment sessions per day during waking hours. Each breath delivers 6 mcg of treprostinil. The initial dose is three breaths (18 mcg) per treatment session. If not tolerated, the dose may be reduced to one to two breaths per session and then increased to three. Tyvaso should be increased by three breaths every 1 to 2 weeks until nine breaths (54 mcg) per treatment session is reached. Tyvaso DPI is a single-dose plastic cartridge containing 16, 32, 48, or 64 mcg. The dry agent is increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals. The target maintenance dosage is usually 48 mcg to 64 mcg per session or the highest tolerated without side effects.

Precautions

Tyvaso has not been studied in patients with underlying lung disease (e.g., asthma, COPD). Tyvaso may cause bronchospasm. This agent should not be mixed with any other agents.

RESPIRATORY CARE ASSESSMENT OF SYNTHETIC ANALOGS OF PROSTACYCLIN

Respiratory care assessment of prostacyclin (PGI₂) agents is directed primarily at lung function. These agents are capable of causing bronchospasm. Assessment of the lungs for the frequency and severity of bronchospasm is the most important step in the management.

Before Treatment

- Assess walking distance.

During Treatment and Short Term

- Monitor ventilatory and cardiovascular status.

Long Term

- Monitor effects of agents on improvement in walking distance.

General Contraindications

- PGI₂ agents have not been tested in patients with underlying pulmonary disorders.

Phosphodiesterase 4 Inhibitor

Roflumilast (Daliresp)

Roflumilast is a selective phosphodiesterase 4 (PDE4) inhibitor used to reduce the risk of exacerbations in patients with severe COPD. Phosphodiesterase (PDE) are enzymes that participate in the signaling of activation of chemical in cells (see [Chapter 2](#)). There are a family of PDE enzymes and PDE4 is one member that appears to work on breaking down cAMP. The reduction in cAMP will increase proinflammatory mediators, possibly causing issues in the lung. PDE4 stops the breakdown of cAMP. The inhibition of cAMP increases the amount of cAMP that may produce anti-inflammatory responses in the lungs,⁴⁸ therefore reducing exacerbation in patients suffering from COPD. This agent is not a bronchodilator and should not be used for acute treatment.

Indication for Use

Roflumilast is a selective phosphodiesterase 4 inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The Gold COPD evidence-based strategy list roflumilast as an add on in group D.⁴⁹

Dosage and Administration

Starting treatment with a dose of 250 mcg once daily for 4 weeks and increasing to 500 mcg once daily thereafter may reduce the rate of treatment discontinuation in some patients. The maintenance dose for patients with COPD is one 500 mcg tablet per day, with or without food.

Precautions

The most serious adverse reaction is alteration in mental status that may lead to suicidal behavior. Cautioned use in patients that have mental illness or suffer from depression. However, change in mental behavior can occur from use of the agent if patients do not have a history of mental instability. Additional adverse reactions include weight loss, diarrhea, nausea, and headache.

RESPIRATORY CARE ASSESSMENT OF PHOSPHODIESTERASE 4 INHIBITOR

Respiratory care assessment of a phosphodiesterase 4 inhibitor should be directed at exacerbation history of the patient. Utilization of the GOLD COPD strategy along with the patient's history to determine best course of action. This agent does not treat bronchospasm.

Before Treatment

- Assess PFT.
- Assess exacerbation history.

During Treatment and Short Term

- Monitor mental status.

Long Term

- Monitor improvement in exacerbations.
- Continue monitoring mental status.

General Contraindications

- Mental status; see precautions above.

Cystic Fibrosis Transmembrane Conductance Regulators

Cystic fibrosis transmembrane conductance regulators (CFTR) were developed to assist the CFTR gene to correct a defective protein. The CFTR protein balances the flow of water and chloride in the cell lining of organs such as the lungs. If a CFTR protein malfunctions or is nonexistent it creates a buildup of viscous mucus. The agents developed and approved by the FDA are orphan drugs (see [Table 16.3](#)). These agents are only effective in individuals with specific mutations. Currently the FDA has approved four different CFTR modulators, each with a specific mutation to assist.⁵⁰

Indication for Use

A specific mutation in the CFTR gene or mutation that shows responsiveness. For unknown genotypes a CF mutation test should be used to detect a CFTR mutation.

Dosage and Administration

Dosage and administration of CFTR varies, see [Table 16.3](#).

Precautions

Elevated liver enzymes are possible. Monitoring transaminase levels before and during use of CFTR agents. A baseline eye

examination is highly recommended as CFTR agents may cause cataracts.

RESPIRATORY CARE ASSESSMENT OF CFTR AGENTS

Respiratory care assessment of CFTR is determined by the health of the CF patient and any mutations that may exist to improved CF symptoms. These agents do not treat bronchospasm. The assessment for respiratory care is more focused on the overall pulmonary evaluation of the CF patient, no matter the use of CFTR agents. However, monitoring of pulmonary function values will be helpful.

TABLE 16.3 Cystic Fibrosis Transmembrane Conductance Regulators

Generic	Brand	Dosage	Mutation
Ivacaftor	Kalydeco	Tablet: Adults and children age 6 years and older: one 150 mg every 12 hours Granules*: Children 4 months to less than 6 months of age and ≥ 5-kg: one 25-mg packet every 12 hours Children 6 months to less than 6 years of age and 5 kg ≤ 7 kg: one 25-mg packet every 12 hours Children 6 months to less than 6 years of age 7 kg ≤ 14 kg: one 50-mg packet every 12 hours Children 6 months to less than 6 years of age and >14 kg: one 75-mg packet every 12 hours	G551D
Lumacaftor/ivacaftor	Orkambi	Tablet: Adults and children age 12 years and older: two tablets each containing lumacaftor 200 mg and ivacaftor 125 mg taken every 12 hours Granules*: Children 4 months to less than 6 months of age and ≥ 5 kg: one 25-mg packet every 12 hours Children 6 months to less than 6 years of age and 5 kg ≤ 7 kg: one 25-mg packet every 12 hours Children 6 months to less than 6 years of age and 7 kg ≤ 14 kg: one 50-mg packet every 12 hours Children 6 months to less than 6 years of age and >14 kg: one 75-mg packet every 12 hours	Homozygous F508del
Tezacaftor/ivacaftor	Symdeko	Tablet: Children 6 to less than 12 years weighing <30 kg: one tablet each containing tezacaftor 50 mg/ivacaftor 75 mg in AM and one tablet containing ivacaftor 75 mg in PM, approximately 12 hours apart Adults and children 12 years and older or children age 6 to less than 12 years weighing >30 kg: one tablet each containing tezacaftor 100 mg/ivacaftor 150 mg in the AM and one tablet, containing ivacaftor 150 mg in PM, approximately 12 hours apart	Homozygous F508del, and 154 other mutations.
Elexacaftor/tezacaftor/ivacaftor	Trikafta	Tablet: Children 6 to less than 12 years weighing <30 kgs: two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg in AM and one tablet of ivacaftor 75 mg in PM Children 6 to less than 12 years weighing >30 kgs: two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in AM and one tablet of ivacaftor 150 mg in PM Adults and children 12 years and older: two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in AM and one tablet of ivacaftor 150 mg in PM	One F508del, and 158 other mutations

*Granules should be first mixed with 1 teaspoon liquid or soft food before dispensing.

Note, all medication in this table should be taken with fat-containing food.

Insulin Human (Recombinant DNA Origin)

Insulin Human (Afrezza)

CLINICAL CONNECTION

Afrezza is an inhaled form of insulin that can cause bronchospasm. It is not recommended for use in patients with lung disease.

Until recently, individuals diagnosed with diabetes had two common formulations to regulate insulin production and control sugar: oral medications or injectable insulin. Several years ago, Exubera, an orally inhaled insulin, was made available; however, Pfizer voluntarily removed it from the market in 2007 because of poor sales. Pfizer lost \$2.8 billion in the research, development, and launch of the product. In 2014, the FDA approved Afrezza, an inhaled human insulin utilizing a dry powder cartridge from the Afrezza Inhaler. Although this is not a respiratory medication, side effects, such as bronchospasm and reduction in lung function, are possible. The respiratory therapist should be aware of its use and inhaled formulation.

Indication for Use

Afrezza is indicated to improve glycemic control in adult patients with diabetes mellitus. Afrezza is not a replacement for long-acting insulin and should be used in combination in patients with type 1 diabetes.

Dosage and Administration

Afrezza is available in 4-, 8-, and 12-unit inhaled dosages. It should be used before mealtime. Dosage is individualized and should be adjusted when switching from another form of insulin.

Precautions

Afrezza has not been tested in patients who smoke or those who have lung disease. Therefore, patients with a history

of smoking and lung disorders should not use this form of insulin.

RESPIRATORY CARE ASSESSMENT OF INHALED INSULIN

Respiratory care assessment of inhaled insulin therapy is directed primarily at lung function. Afrezza may cause bronchospasm and exacerbation of lung disease. In patients not known to have pulmonary dysfunction, a decline in pulmonary function has been noted.⁵¹ Assessment of breath sounds in the lungs for frequency and severity of bronchospasm is the most important.

Before Treatment

- Assess lung health; does patient have lung disease?
- Smoking status should be monitored; patients who smoke should not take the drug.

During Treatment and Short Term

- Monitor airway status; listen for abnormal breath sounds.

Long Term

- Monitor effects of agents on lung function.
- Overall pulmonary health should be assessed on the basis of frequency and severity of respiratory infections, cough, bronchospasm, and pulmonary function.

General Contraindications

- Patients with a history of smoking and lung disorders should not use this form of insulin.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. For which disease state is an α_1 -proteinase inhibitor (API) indicated?
2. What is the route of administration for an API?
3. What is the mode of action of APIs in treating emphysema associated with inadequate API levels?
4. Is treatment with an API indicated for age-related emphysema or in general for individuals who smoke and have emphysema later in life?
5. Identify three pharmaceutical formulations of nicotine that are used as smoking cessation aids.
6. What is the usual effect of nicotine, whether in a smoking cessation aid or in cigarettes, on blood pressure?
7. Name two nonnicotine agents used in the treatment of smoking cessation.
8. What is the effect of inhaled nitric oxide (NO)?
9. Identify two potentially toxic byproducts of inhaled NO.
10. What is the usual dose of inhaled NO?
11. Identify two disease states in which NO has been used to reverse pulmonary hypertension.
12. What is the greatest hazard in terms of pulmonary health with the delivery of Ventavis?
13. What is the initial dose of Tyvaso?
14. When in the COPD evidence-based strategy should roflumilast be utilized?
15. What are the four CTFR agents approved for use in the US?
16. What is the trade name of the only inhaled insulin on the market?
17. What patient population should avoid the use of inhaled insulin?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 42-year-old White woman with complaints of shortness of breath on exertion and increasing fatigue during her usual activities was referred by her family physician to a pulmonologist. On questioning, she reported that she had an uncle who had died “many years previously” in middle age as a result of lung disease, but he had been a smoker. She admitted that she had been a heavy smoker (around a pack per day) for 5 or 6 years but had quit more than 8 years ago. She denied any use

of alcohol. She described having several attacks of “bronchitis” in the past year, for which her family physician had prescribed antibiotics, with subsequent resolution each time. She also described small but increasing production of sputum during the past year, usually clear unless she had an episode of bronchitis. She currently has a cough, with occasional production of a slight amount of greenish sputum. Her medications include albuterol via metered dose inhaler (MDI), prescribed by her family physician last year.

CLINICAL SCENARIO—cont'd

On physical examination, she appeared well developed and well nourished and exhibited mild respiratory distress. Auscultation of the chest revealed expiratory wheezing, diminished breath sounds bilaterally, and a prolonged expiratory phase. No digital clubbing, cyanosis, pedal edema, or jugular distention was noted. Her vital signs were as follows: temperature (T) 37.1°C, blood pressure (BP) 110/76 mm Hg, pulse (P) 76 beats/min, and respiratory rate (RR) 24 breaths/min and regular. Pulse oximetry on room air was 91%. Other findings included a mild elevation of white blood cell (WBC) count ($13.1 \times 10^3/\text{mm}^3$), normal hemoglobin and hematocrit, and normal electrolytes. *Pseudomonas* and normal flora were found in her sputum. A chest radiograph showed some hyperlucency; hyperinflation

with moderately lowered, flattened hemidiaphragms on full inspiration; and an infiltrate in the right lower lobe. Arterial blood gas (ABG) values on room air were as follows: pH 7.35, PaCO_2 54 mm Hg, PaO_2 66 mm Hg, HCO_3^- 30 mEq/L, and SaO_2 92%. Pulmonary function tests showed forced expiratory volume in 1 second (FEV_1) at 60% of predicted, elevated residual volume (RV) and RV/total lung capacity (TLC) ratio, increased TLC above predicted, and decreased DL_{CO} (diffusing capacity of the lungs for carbon monoxide [CO]).

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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17

Neonatal and Pediatric Aerosolized Drug Therapy

RUBEN D. RESTREPO

CHAPTER OUTLINE

Off-Label Use of Drugs in Neonatal and Pediatric Patients

Factors Affecting Neonatal and Pediatric Aerosol Drug Delivery

Effect of Age on Aerosol Lung Dose

Effect of Small Tidal Volumes, Short Respiratory Cycles, and Low Flow Rates

Effect on Small Volume Nebulizer

Effect on Reservoir Dose

Nebulized Drug Distribution

Clinical Response to Aerosolized Drugs in Neonatal and Pediatric Patients

Selection of Delivery Devices

Nebulizers

Pressurized Metered Dose Inhalers

Dry Powder Inhalers

Use of Selective Agents in Neonatal and Pediatric Patients

Antibiotics

Mucoactive Agents

Aerosol Surfactants

Antiinflammatory Drugs and Antibiotics

Aerosolized Peptides and Proteins

Prostacyclin Analogs for Pulmonary Hypertension

Adherence, Compliance, and Cooperation During Aerosol Therapy

Facemasks Design, Fitting, Crying, and “Blow-By”

High-Flow Nasal Cannula

Nebulizer Hood

Parent Education on Inhalation Therapy

Aerosol Administration in Intubated Neonatal and Pediatric Patients

Summary

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to neonatal and pediatric drug therapy
2. Explain off-label use of aerosolized medications in neonates and children
3. List and describe the most important factors affecting neonatal and pediatric aerosol drug delivery
4. Describe the clinical response of neonatal and pediatric patients to aerosolized drugs
5. Describe special circumstances related to selection of delivery devices for neonatal and pediatric patients
6. Explain the most relevant factors to select the appropriate aerosol delivery device according to age group
7. Describe the implications of compliance and cooperation on the efficiency of aerosol delivery
8. List some of the novel inhaled therapies under investigation for pediatric patients
9. Explain the importance of parent education in the administration of inhalation therapy to children
10. Explain lung deposition of inhaled drugs in pediatric and neonatal intubated patients

KEY TERMS AND DEFINITIONS

Emitted dose Dose released by aerosol device.

Infant Child between 1 month and 1 year of age.

Inhaled (delivered) dose Dose reaching the patient's mouth or artificial airway.

Lung dose Dose reaching the trachea and beyond.

Neonatal Refers to the period between birth and first month of life.

Nominal dose Dose in delivery device.

Off-label Use of drugs with no US Food and Drug Administration (FDA)-approved labeled use.

Pediatric Refers to the period between ages 1 month and 18 years.

Pediatric patients with airway disease depend on inhaled medications. However, effective administration of aerosol therapy to neonates and pediatric patients is challenging because the efficiency of delivery of pharmaceutical aerosols to the lungs of these patients is known to be low and highly variable. Inherent anatomic, physiologic, pathophysiologic, and behavioral factors make this age group a unique subpopulation.^{1,2} The lack of **neonatal** and **pediatric** dose labeling for many drugs given by inhaled aerosol complicates determining proper doses of aerosol drugs. The number of studies on the clinical deposition of aerosols in pediatric subjects, particularly in the neonatal population, is very limited because of the inability to use radiolabeled aerosols. Labeling aerosol particles with radioactive agents makes it possible to quantify deposition dose and distribution in the respiratory tract. The available results of the few lung deposition studies performed in infants are strikingly similar, showing only 2% to 5% deposition.³ Results of studies on therapeutic aerosols and their deposition in adult lungs cannot simply be extrapolated to pediatric cases. The differences between aerosol delivery as a form of topical administration and systemic administration are not appreciated in many instances, causing aerosol doses to be modified in neonates and children based on dosage for systemic administration. Neonates and toddlers do not have the ability to perform the inhalation maneuver; they are usually nasal breathers and often get distressed during administration of aerosol therapy.

Both the prescribing physician and the respiratory therapist need to be aware that the anatomic and physiologic characteristics of this age group must be matched with the proper devices and techniques of administration. Even after an optimal device has been selected, such factors as crying, lack of cooperation, and presence of leaks around the aerosol masks can dramatically decrease lung deposition. Identification of the determinants of efficient aerosol delivery and the specific challenges of aerosol delivery to infants and young children can help determine a systematic approach to optimizing aerosol delivery to this population. All considerations in this chapter relate to inhaled aerosols used for the treatment of pulmonary disorders and not for systemic treatment. The data cited are based largely on traditional aerosol delivery devices. New, highly efficient delivery systems may yield different results in the future. Terms used for different age ranges are given in [Box 17.1](#).

Off-Label Use of Drugs in Neonatal and Pediatric Patients

KEY POINT

Pediatric patients are the most common group to be prescribed off-label use medications.

• BOX 17.1 Terms and Age Ranges Defining Periods From Birth to Adulthood

Premature neonate	Less than 37 weeks of gestational age
Neonate	First month of postnatal life
Infant	1–12 months
Child	1–12 years
Adolescent	12–18 years
Adult	Older than 18 years

The term **off-label** refers to using an approved drug for an unapproved use to treat a disease or medical condition (e.g., use of aspirin for prophylaxis of heart attack—approved use: pain reliever). Prescribing off-label medications is common due to a lack of pediatric-specific data regarding the dosing, efficacy, and safety of medications regularly prescribed to children. It has been estimated that off-label prescriptions in children range from 3.2% to 95%.⁴ Before the US Food and Drug Administration (FDA) intervention, only about 20% of drugs approved were label for pediatric use. Since 1997, the FDA has promoted legislation that has led to a dramatic increase in pediatric studies submitted to the FDA and hundreds of medications with new pediatric information in labeling ([Table 17.1](#)).^{5,6}

Today, greater than 50% of all currently marketed drug products include pediatric information on their product labeling. Additionally, not only medications but also medical devices need to be approved for pediatric use. That is why in September 2007 the United States Congress passed Title III of the FDA Amendments Act—the Pediatric Medical Device Safety and Improvement Act—requiring that new applications or protocols submitted to the FDA for the use and approval of a medical device must include a description of any pediatric subpopulation that suffers from the condition and will be treated, diagnosed, or cured by such device.

Although it is legal for physicians to prescribe off-label use of drugs, determining the dosage becomes more problematic when standardized guidelines have not been developed during clinical trials. Generally, regimens for inhaled aerosols for neonatal and pediatric patients are not based on body size and blood level but rather on a target effect strategy with avoidance of toxicity. Aerosol doses to neonates or children are “self-limiting” because of the differences between pediatric and adult airways. Many of the inhaled aerosol drugs reviewed in this text have clinical indications and uses in neonatal and pediatric patients, even though their product labels often state that safety and efficacy in children have not yet been determined.

[Table 17.2](#) lists inhaled aerosol drugs and leukotriene modifiers that have approved age labeling for pediatric use at the time of this edition. Drugs that are not listed in [Table 17.2](#) do not have the labeling for pediatric use.

Factors Affecting Neonatal and Pediatric Aerosol Drug Delivery

KEY POINT

Although a smaller fraction of the aerosol reaches the pediatric lower airway compared with the adult airway, the need for clinical adjustment of aerosol doses based on age and body weight is still being debated.

The mechanisms of aerosol penetration and deposition in the adult lung, as outlined in [Chapter 3](#), also apply to aerosol therapy in neonatal and pediatric patients. However, the airway environment differs in neonatal and pediatric subjects compared with that in adults. The diameter of the airway is smaller in newborns, infants, and small children. Besides cooperation, ability to hold a mouthpiece, and avoidance of mouth breathing, the obvious limitations of inspiratory flow can greatly affect aerosol delivery and deposition. Pediatric patients are either obligate or preferential nose breathers, have a proportionally larger tongue, and have smaller and incompletely developed airways compared with adults. In addition, nasal airway resistance accounts for nearly

TABLE 17.1 Overview of Federal Legislation to Promote Pediatric Studies

Legislation	Year Enacted	Implications
Food and Drug Modernization Act (FDAMA)	1997	Encouraged pharmaceutical manufacturers to perform pediatric studies Offered 6 months patent exclusivity as financial incentive
Pediatric Rule	1998	Required efficacy & safety testing for NDAs if medication could be used in children Studies under Pediatric Rule were eligible for a 6-month patent extension under FDAMA Federal court overturned in 2002 because FDA did not have authority
Best Pharmaceuticals Act for Children (BCPA)	2002	Authorized FDA to request pediatric studies with NDAs (including orphan drugs) for new indications Extended the 6-month patent exclusivity through 2007 Required NIH to publish list of needs for future study in children
Pediatric Research Equality Act (PREA)	2003	Required pediatric assessment & development of PSP with NDAs (expanded version of Pediatric Rule) for certain drugs (NOT orphan drugs) Allowed for modifications to existing indications Pediatric plan must be developed before approval in adults
Food and Drug Administration Amendments Act (FDAAA)	2007	- Reauthorized PREA & BCPA × 5 years - Expanded the BCPA so FDA could issue request for > 1 indication (i.e., “on” & “off-label” use) - Introduced Pediatric Medical Device Safety & Improvement Act
Food and Drug Administration Safety and Administration Act (FDASIA)	2012	Made BCPA & PREA permanent

half of the respiratory resistance in healthy infants,³ and turbulent flow in this region likely accounts for a large amount of impactive drug loss in the upper airways. These differences produce flow characteristics different from those in adults. Table 17.3 outlines the functional and structural features of the infant lung that may affect aerosol delivery and deposition.

Although it may seem obvious that aerosol therapy in infants and young children is quite different from that in adults, much more research is required to confirm the differences in aerosol drug delivery. Some in vitro studies have suggested that the increasing upper airway geometry in adults may explain the higher amount of aerosol deposition reaching the lower airway compared with that in neonatal and pediatric patients.⁷ The nose may filter out 75% of the dose received by mouth breathing in adults and children. A smaller fraction of the **nominal dose** of an aerosol reaches the lower airways with the child-size oropharynx compared with an adult-size oropharynx.⁸ The oral route has been considered superior to the nasal route for aerosol delivery to the lower respiratory tract (LRT) in adults and children. However, this may not be the case in infants. Amirav et al.⁹ used radiolabeled normal saline solution aerosol generated by a soft-mist inhaler and aerosol delivered via a valved holding chamber (VHC) and an air-tight mask to a simulated 5- to 20-month-old airway model. They found that nasal delivery to the LRT exceeded that of oral delivery in the 5- and 14-month models and was equivalent to oral delivery in the 20-month model and that differences between nasal and oral delivery diminished with “age”/size.¹⁰ The smaller diameter of the neonatal and pediatric lower airways, added to the effects of bronchoconstriction, inflammation, secretions, and the possible presence of an endotracheal tube, dramatically decreases aerosolized drug deposition in the lungs.¹¹ Some other variables associated with the reduction in **lung dose** in infants and young children are discussed below.

Effect of Age on Aerosol Lung Dose

Systemic side effects, rather than local side effects caused by treatment in the lung, have been the basis for aerosol dose adjustment for age, which is usually based on body weight. However, the need

for clinical adjustment of aerosol doses based on age and body weight is being debated.^{12,13}

The optimal particle size of aerosols that will enhance intrapulmonary deposition in pediatric patients breathing through either artificial airways or the oronasal region is unknown. In in vivo studies, experimental data obtained during spontaneous unassisted breathing have demonstrated that 3% of the nominal dose of aerosolized drugs is delivered to the lungs of infants; 1.6% to 4.4% to those of young children; and 10% to 58% to those of adults.¹⁴ Although a smaller percentage of the aerosol is deposited in the lungs, small patients may receive a considerably higher rate of drug per kilogram of body weight compared with adults. However, the lower deposition may provide a safety and efficacy profile comparable with that in adults.¹

A report by Anhoj et al. has suggested that the **inhaled (delivered) dose** need not be adjusted for age to reduce systemic levels and possible toxicity since the dose reaching the lung is proportionally less for younger smaller subjects.¹⁵ Nebulized albuterol doses recommended by expert consensus guidelines for exacerbations in children 12 years of age or older are 0.15 to 0.3 mg/kg up to 10 mg every 1 to 4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.¹⁶ When a fixed dose of 2.5 mg delivered by nebulizer was compared with a dose of 0.1 mg/kg body weight in children with acute asthma 4 to 12 years of age, there was no difference between the two dose protocols in clinical improvement measured by flows, oxygen saturations, and clinical score or in cardiovascular and tremor side effects. The fixed dose of 2.5 mg by nebulizer was efficacious and safe.¹⁷ Hosseinezhad and Abbasi concluded that there is no advantage in the routine administration of albuterol at doses higher than 2.5 mg for patients with acute asthmatic attacks.¹⁸

Effect of Small Tidal Volumes, Short Respiratory Cycles, and Low Flow Rates

Small pediatric patients have low tidal volumes, low vital capacities, short respiratory cycles, and low inspiratory flow rates. Children inhale a smaller percentage of the **emitted dose** from either a small volume nebulizer (SVN) or a pressurized metered dose inhaler (pMDI) with

TABLE 17.2 Pediatric Drug Labeling for Inhaled Aerosols and Leukotriene Modifiers*

Drug Name	Formulation	Age Labeling (FDA Approved)
<u>β-Adrenergic Agents</u>		
Albuterol	MDI SVN DPI	≥4 yr: 2 inhalations q4-6h; 2-12 yr: 1.25-2.5 mg tid-qid [†] ≥4 yr: 1-2 inhalations q4-6h
Levalbuterol	MDI SVN	≥4 yr: 2 inhalations (90 mcg) q4-6h 6-11 yr: 0.31 mg tid; maximum 0.63 mg tid
Racemic epinephrine	SVN	≥4 yr: 0.5 mL of 2.25% solution in 3 mL diluent; q3-4h
<u>Corticosteroids</u>		
Beclomethasone	MDI	≥5 yr: 40-80 mcg twice daily
Budesonide	DPI SVN	≥6 yr: 180-360 mcg bid; 12 mo-8 yr: 0.5 mg total daily dose given once or twice daily in divided doses; maximum 1 mg total daily given once or 0.5 mg twice daily
Flunisolide	MDI	6-11 yr: 80 mcg twice daily, no more than 160 mcg twice daily
Fluticasone	DPI MDI	≥4 yr: 50 mcg twice daily up to 100 mcg twice daily; 4-11 yr: 88 mcg bid
Fluticasone propionate/salmeterol	DPI	≥4 yr: 100 g fluticasone/50 g salmeterol, 1 inhalation twice daily, about 12 hr apart
Mometasone furoate	MDI	≥4 yr: 220 mcg daily
Mometasone/formoterol	MDI	≥12 yr: 200 mcg twice daily
Ciclesonide	MDI	≥12 yr: 160 mcg twice daily
<u>Mucoactive Agent</u>		
Dornase alfa	SVN	Safety and efficacy in children <5 yr have not been studied; usual dose 2.5 mg once daily
<u>Nonsteroidal Antiasthma Agent</u>		
Cromolyn sodium	SVN	≥2 yr: 20 mg tid-qid
<u>Inhaled Antiinfectives</u>		
Aztreonam	SVN (Altera)	75 mg TID, alternate 28 days on, 28 days off
Ribavirin	SPAG	<i>Infants and young children:</i> a 20 mg/mL solution nebulized for 12-18 hr/day for 3-7 days
Tobramycin	SVN	≥6 yr: 300 mg bid, alternate 28 days on, 28 days off
Colistin [‡]	SVN	≥6 yr: 75 mg or 150 mg twice daily
<u>Leukotriene Modifiers</u>		
Montelukast	PO	12-23 mo: one packet of 4-mg oral granules daily in the evening; 2-5 yr: one 4-mg chewable tablet daily in evening or one packet of 4-mg oral granules daily in the evening; 6-14 yr: one 5-mg chewable tablet daily in evening
Zafirlukast	PO	5-11 yr: one 10-mg tablet bid
Zanamivir	DPI	≥5 yr: 2 inhalations bid for 5 days
<u>Bronchial Challenge</u>		
Mannitol	DPI	>6 yr

*Additional detail on dosing for adults can be found in previous chapters. Manufacturers' information and other sources on drug administration and dosing should be consulted before use. Drug labeling is current at the time of this edition.

[†]Most frequent administration is not recommended. Patients 6 to 12 years of age with more severe asthma (baseline FEV₁ <60% predicted), patients with weight greater than 40 kg, or patients 11 to 12 years of age may achieve a better initial response with higher dose.

[‡]Colistin is used off-label for nebulization and is not FDA approved for inhalation.

bid, Twice daily; DPI, dry powder inhaler; MDI, metered dose inhaler; PO, by mouth; qid, four times daily; SPAG, small particle aerosol generator; SVN, small volume nebulizer; tid, three times daily.

TABLE 17.3 Comparison of Neonatal and Adult Respiratory Parameters

Parameter	Neonate	Adult
Tracheal diameter	≈4 mm	≈20 mm
Tracheal length	5–6 cm	10–12 cm
Tidal volume	6 mL/kg	6 mL/kg
Respiratory rate	30–40/min	12–14/min
Minute ventilation	200–300 mL/kg/min	6 L/min
Dead space	0.75 mL/lb	1.0 mL/lb
Inspiratory flow rate	≤100 mL/sec	≈500 mL/sec

From Kacmarek, R., Stoller, J. K., & Heuer, A. H. (Eds.) (2020). *Egan's fundamentals of care* (12th ed.). St. Louis, Missouri: Elsevier.

a reservoir device (holding chamber or spacer). The aerosol deposition is reduced because of a shorter transit time for small particles in the airways. These factors can significantly alter the inhaled dose and the lung dose of patients younger than 6 months of age.

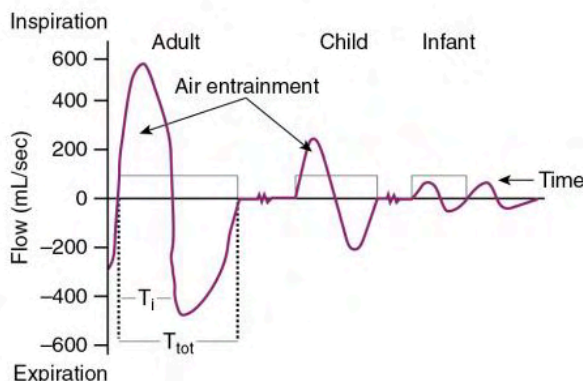
Effect on Small Volume Nebulizer

If we assume a 6 L/min power gas, an adult with inspiratory flow of 500 mL/sec (30 L/min) and a tidal volume of 500 mL (500 mL/sec × 1 or 2 seconds) would completely inhale all the nebulizer output. However, an **infant** with inspiratory flow of less than 100 mL/sec (<6 L/min) and a tidal volume less than 100 mL would not completely inhale all the nebulizer output during the inspiratory phase (Fig. 17.1).

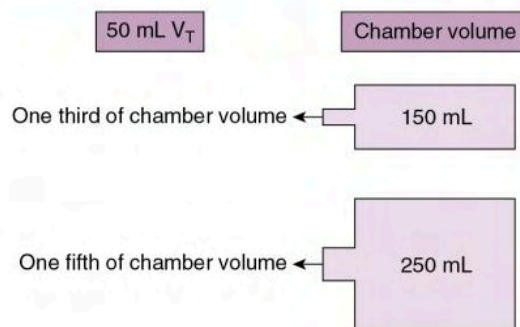
Several authors have demonstrated that the fraction of nebulizer output inspired is lower in infants younger than age 6 months and that the inhaled aerosol dose from an SVN attached to a mask increases as the weight in infants increases.¹⁹

Effect on Reservoir Dose

The same effect of low tidal volumes would theoretically reduce the amount of volume and drug mass inhaled from a reservoir chamber (Fig. 17.2). The amount of reduction is proportional to the chamber volume for a given infant tidal volume. For a 50-mL tidal volume, approximately one third (33%) of a 150-mL chamber and



• **Fig. 17.1** Illustration of the amount of nebulizer output inspired with varying inspiratory patterns (volumes, flow rates, times), indicating a smaller fraction of output inspired with low tidal volumes and flow rates in infants compared with adults. T_i , Inspiration time; T_{tot} , total cycle time. (From Collis, G. G., Cole, C. H., & Le Souef, P. N. [1990]. Dilution of nebulised aerosols by air entrainment in children. *Lancet*, 336, 341.)



• **Fig. 17.2** Conceptual illustration of the effect of small tidal volumes (V_T) on chamber evacuation with different-size reservoir chambers.

one fifth (20%) of a 250-mL chamber would be inhaled. Even assuming no redistribution of aerosol in the chamber volume, gravitational settling would reduce the available dose further within seconds of pMDI actuation into the chamber. The ideal volume for a spacer device is small enough to allow for drug inhalation with few breaths in infants with low tidal volumes (<50 mL).²⁰

Data from Everard et al. on delivery (not lung deposition) of pMDI cromolyn sodium via reservoir and facemask with tidal volumes of 25, 50, and 150 mL were measured in vitro by using various sizes of chambers. Smaller tidal volumes were associated with decreased inhaled drug mass. Higher aerosol concentrations in a smaller chamber enhanced drug delivery with tidal volumes less than 150 mL.²¹ Introduction of dead space between the chamber outlet and the filter collecting inspired drug reduced the dose deposited by 50% or greater.

Measurements of lung deposition of radiolabeled albuterol delivered through a pMDI and antistatic spacer with facemask or mouthpiece in children with stable asthma have revealed that mean lung deposition (% total dose) could be significantly higher with the mouthpiece.²²

Such variation in study results indicates that testing conditions, type of drug, and choice of reservoir device can affect inhaled dose, although not necessarily the lung dose. **Box 17.2** lists factors

• BOX 17.2 Factors That May Affect Dose Inhaled From a Reservoir Chamber in Neonatal and Pediatric Patients

Mechanical and Design Factors

- Chamber volume
- Electrostatic charge on plastic devices
- Shape of aerosol plume relative to chamber size
- Design of inspiratory and expiratory valves, if present
- Presence of inspiratory valve
- Amount of dead volume in mouthpiece

Patient Factors

Anatomic

- Larger tongue in proportion to oral airway
- Smaller airway diameter
- Smaller number of alveoli

Breathing Pattern

- Nasal breathing
- Inability to hold mouthpiece

Inspiratory Flow Rate

- Tidal volume

in reservoir devices that may affect the inhaled dose in neonates, infants, and small children.

Nebulized Drug Distribution

It might be obvious to the respiratory clinician that outcomes of aerosol therapy in young children are quite different from those in adults and that much more research is required to confirm the differences in aerosol drug delivery. The most definitive data for answering the question as to how much aerosol drug reaches the lungs of neonates and pediatric patients are actual measures of lung deposition. However, radiolabeled deposition and pharmacokinetic studies of inhaled drugs are challenging in pediatric medicine. Most radiolabeled substances used to estimate lung deposition may be harmful to children; thus, most of the available data come from in vitro studies.²² Some available data indicate that the lung dose of an aerosol drug does, in fact, decrease with age. Anhoj et al. found that blood levels of drug, reflecting the dose reaching the lungs, were constant in younger and older subjects despite the smaller circulating volume in younger patients.¹⁵

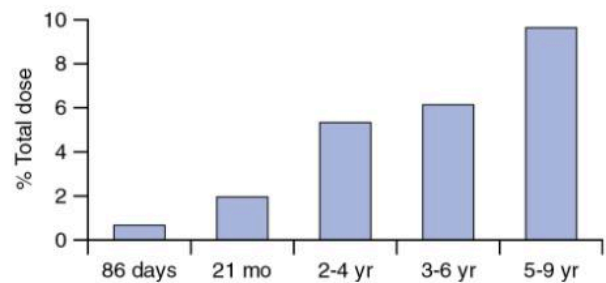
It has been hypothesized that the greater the infant's distress, the lower is the lung deposition and the higher is the upper respiratory tract and gastrointestinal tract depositions. Evaluation of distribution of nebulized bronchodilators in wheezing infants has shown an average of 10% to 12% adherence to the patient's face, $7.8\% \pm 4.9\%$ deposition in the upper respiratory and gastrointestinal tracts, and $1.5\% \pm 0.7\%$ deposition in the lungs (Fig. 17.3).^{23,24}

Fig. 17.4 summarizes data on lung deposition with inhaled aerosols compiled from four studies. All the studies used a pMDI with a reservoir device and a facemask for delivery in subjects younger than 4 years. Values represent the percentage of total dose from the device.

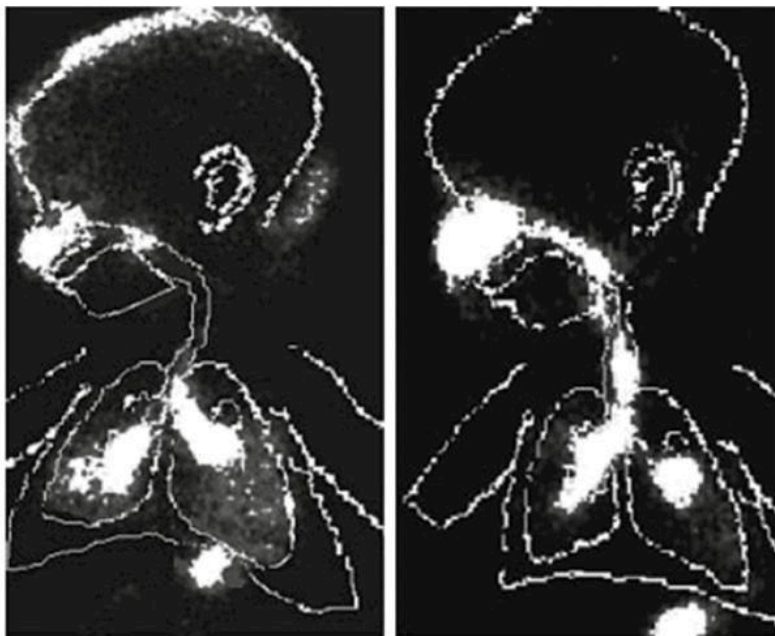
Tal et al. found a mean of 1.97% (SD 1.4) as a lung dose of albuterol in patients with a mean age of 21 months (range 3 months to 5 years).²⁵ Wildhaber et al. found 5.4% (SD 2.1) and 9.6%

(SD 3.9) of albuterol reached the lungs of 2- to 4-year-olds and 5- to 9-year-olds.²⁶ A previous study using indirect measures of plasma levels found that 6.1% of a budesonide dose reached the lungs of 3- to 6-year-olds.²⁷

Using the amount of aerosolized albuterol reaching the lungs of infants and children in the study by Tal et al.,²⁵ it can be shown that the self-limiting effect of younger ages on lung dose results in the same dose per amount of body weight in children as in adults (Table 17.4). The equivalence of dose per body weight, as illustrated in Table 17.4 and based on lung deposition data, argues strongly against the need to adjust the nominal dose of an aerosol drug for age or body size with current aerosol delivery devices. Age and size have a self-limiting effect on lung dose, producing a natural titration of dose. This conclusion may need to be revised with introduction of more efficient aerosol delivery devices.



• **Fig. 17.4** Percent of total aerosol dose that reaches the lungs of infants and children of varying ages. Aerosol dose was delivered by using a metered dose inhaler with a reservoir device and a facemask in subjects younger than 4 years of age. Studies shown are Fok et al.¹¹⁵ for 86 days, Tal et al.²⁵ for 21 months, Wildhaber et al.²⁶ for 2 to 4 years and 5 to 9 years, and Agertoft et al.²⁷ for 3 to 6 years.



Hood

Mask

• **Fig. 17.3** Scan of patient obtained during hood and mask treatments showing deposition of aerosolized medication in the upper respiratory tract (URT) and in the gastrointestinal (GI) system. Note the considerably higher URT and GI depositions with mask treatment. (From Amirav, I., Balanov, I., Gorenberg, M., et al. [2003]. Nebuliser hood compared with mask in wheezy infants: aerosol therapy without tears. *Archives of Disease in Childhood*, 88, 719–723.)

TABLE 17.4 Calculation of Dose per Kilogram of Aerosolized Albuterol for Children and Adults Based on Lung Deposition Data (1.75%) Showing Equivalence of Dose per Body Size

	Adult	Child
Weight	60 kg	10 kg
Lung deposition	20%*	2%
Nominal dose	200 mcg	200 mcg
Dose to lung	40 mcg	4 mcg
Per kilogram dose	0.5 mcg/kg	0.4 mcg/kg

*Percentage lung disposition measured by Tal et al. in two adult volunteers in the same study. Data from Tal, A., Golan, H., Grauer, N., et al. (1996). Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *Journal of Pediatrics*, 128, 479.

Clinical Response to Aerosolized Drugs in Neonatal and Pediatric Patients

CLINICAL CONNECTION

Crying and distress, even with the best-designed facemask, can seriously affect the efficiency of aerosol administration in young children.

The lung deposition data reviewed in the previous section argue that aerosolized drugs reach the lungs of infants in a self-regulating amount. The question of clinical response to aerosol drugs in infants and pediatric patients is not determined by lung deposition data. The most studied drug class—one of great interest in neonates and infants—is the adrenergic bronchodilator group. Compared with corticosteroids, the clinical response to bronchodilator occurs within minutes and is more feasible to study in young subjects.

Commonly cited studies from the late 1970s concluded that response to inhaled bronchodilators was lacking in infants and children younger than 18 months of age.^{28,29} These studies found no change in respiratory resistance with phenylephrine, epinephrine, or salbutamol (albuterol) in infants and children 7 to 18 months of age with use of a forced oscillation technique. The authors of those studies speculated that there was either poor development of smooth muscle in children younger than 18 months of age or the bronchial obstruction was caused by secretions and airway edema, rather than bronchoconstriction.

Although it has been known that the level of response to a bronchodilator increases significantly with increasing age in young patients with asthma (ages 3 to 9 years), evaluation of ventilated and nonventilated preterm infants has shown dose-related changes in oxygen saturation; respiratory mechanics, including airway resistance; and compliance with aerosolized bronchodilators.^{30,31}

Selection of Delivery Devices

The current methods to deliver therapeutic aerosols can be classified into three categories: (1) nebulizers (jet or ultrasonic); (2) pMDIs that can be used with a press-and-breathe technique, as a breath actuated device, or in combination with a VHC or spacer; and (3) dry powder inhalers (DPIs). Table 17.5 gives guidelines

TABLE 17.5 Age Guidelines for Use of Current Aerosol Delivery Devices

Delivery Device	Age Recommended (yr)
SVN with mask	≤3
SVN with mouthpiece	≥3
pMDI with spacer/VHC and mask	<4
pMDI with spacer/VHC	≥4
DPI	≥5
pMDI	≥5
Breath-actuated MDI	≥5
Breath-actuated nebulizers	≥5

DPI, Dry powder inhaler; MDI, metered dose inhaler; pMDI, pressurized metered dose inhaler; SVN, small volume nebulizer; VHC, valved holding chamber.

Data from National Asthma Education and Prevention Program. (2007). *Expert Panel Report III: guidelines for the diagnosis and management of asthma*. Bethesda, Maryland: National Institute of Health.

for age-dependent use of current aerosol delivery devices in infants and children, based on the 2020 National Asthma Education and Prevention Program (NAEPP) guidelines.³² Either a jet nebulizer or an MDI can be used, with suitable auxiliary devices attached. An evidence-based review by the American College of Chest Physicians determined that for most patients with asthma, SVNs, DPIs, and MDIs are equally effective in delivering short-acting β agonists.^{33,34} Nebulizer systems and pMDI plus spacer are the most suitable aerosol delivery systems for young children because these devices only require tidal breathing for inhalation of the aerosol. Even in acute asthma attacks, delivery of bronchodilators via a pMDI plus spacer is equally effective as nebulizers.³⁵ Nebulizers could be an alternative if the child appears very distressed during use of a pMDI.

Nebulizers

Jet nebulizers used to be the mainstay of aerosol therapy in infants and young children. However, they require a pressurized gas source, bulky equipment, a long treatment period, and additional preparation and cleaning time. A significant disadvantage of nebulizer therapy in children is the poor tolerance often exhibited because of noise of operation and the need for a tight-fitting mask. Although nebulizers may not be used routinely compared with pMDIs, nebulizers are preferred by numerous patients and parents. They are also the preferred delivery device for emerging therapies, such as aerosolized surfactants and antibiotics currently under investigation.^{36–38} With a deposition estimated to be less than 1% in small children and infants, only 25 mcg of a 2.5-mg (2500-mcg) dose will be delivered to the lung.

Despite little evidence for its effectiveness, the breath-actuated nebulizer (BAN) is the default albuterol delivery method in many pediatric emergency departments. Lin and Huang³⁹ compared the therapeutic effects of a BAN and a constant-flow nebulizer (CFN) on 72 patients with asthma, ages 5 to 15 years. These authors found that all the spirometric parameters including forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF), and forced expiratory flow 25% to 75% (FEF_{25%-75%}) and arterial oxygen saturation (SaO₂) at various time points of both groups

improved significantly. In between-group comparison, the BAN group showed greater improvement in all the spirometric parameters and SaO_2 at various time points but only reached statistical significance at some time points in PEF, $\text{FEF}_{25\%-75\%}$, and SaO_2 . Pulse rate in the BAN group was significantly higher than that in the CFN group beginning 5 minutes after treatment.³⁹

A randomized trial of BAN versus continuous 1-hour nebulization and/or a constant-output SVN in pediatric patients with asthma reported that the admission rate with use of BANs was significantly lower (38% versus 57%) and that the BAN group had a significantly greater improvement in clinical asthma score and respiratory rate.⁴⁰ However, recent studies have shown that albuterol therapy by MDI plus spacer produced similar outcomes to BAN for the treatment of mild to moderate asthma exacerbations in children.^{41,42}

Large volume nebulizers (LVNs) are sometimes used in newborns or children in incubators and hoods. Because LVNs produce significant levels of noise, alternative methods to deliver oxygen therapy may be required to reduce the sleep disruption and stress caused by noise levels above 58 decibels (dB). Additional caution needs to be exercised to prevent the use of high fractional inspired oxygen (FiO_2) to power nebulizers in premature newborns to avoid the adverse effects associated with oxygen therapy at this early age.

Pressurized Metered Dose Inhalers

CLINICAL CONNECTION

Pediatric patients utilizing a pressurized metered dose inhaler (pMDI) with a valved holding chamber (VHC) should be allowed to take multiple breaths to empty the chamber because of the smaller tidal volumes.

Use of pMDIs is the method of choice in infants and children younger than 5 years of age, but only when used in combination with an appropriate spacer or VHC.⁴³ A pMDI should not be used without a spacer or VHC even in children 8 years of age or older because most patients are unable to coordinate actuation of the pMDI with the breathing maneuver. An additional advantage of the pMDI and spacer combination is that it considerably reduces the oropharyngeal deposition, which could be as high as 80%, by reducing the velocity of the aerosol jet, thus allowing time for evaporation of the propellants and for the particles to “age” before impacting on a surface. The pMDI delivery system has the advantage of small size, portability, and shorter treatment time, even with an increased number of actuations. However, drug delivery to the lungs via pMDIs can vary greatly, depending on the formulation used and the age of the child. Children 4 to 8 years of age should be encouraged to use a mouthpiece along with the pMDI whenever possible, as a much higher aerosol deposition is seen; a mask attached to the spacer is typically recommended for children younger than 4 years of age. Similar issues about leaks around the mask, as already mentioned for nebulizers, apply to the pMDI–spacer–mask interface.⁴⁴

A recent systematic review and meta-analysis comparing nebulization (NEB) versus MDI with the spacer (MDI+S) in children with severe wheezing or asthma exacerbation showed a significant reduction in the pulmonary index score when using MDI+S.⁴⁵

There are different types of spacers: plastic or metal, with large or small volumes. For children with small tidal volumes, the volume of a spacer is crucial because of the time it takes to empty the spacer. The less time it takes to empty the spacer, the higher is the concentration of aerosol.

As mentioned in Chapter 3, immediately after the aerosol cloud is released from the pMDI, gravitational forces cause sedimentation of aerosol particles onto the spacer wall. This effect is more pronounced when a plastic spacer is used with electrostatic charge. A metal spacer could deliver to the mouth twice the amount of drug compared with a plastic spacer. However, although the electrostatic charge is eliminated with the use of a metal chamber, the simple act of coating a plastic spacer with household detergent minimizes the electrostatic charge and substantially increases lung deposition. The improvement in lung deposition associated with elimination of the electrostatic charge could be seriously compromised by a suboptimal facemask. Recent studies have identified several face-mask factors that determine the success or failure of drug delivery with these VHCs. They include face seal/leak, volume of dead space, contour, flexibility, transparency, weight, and cost.⁴⁶ There is also strong evidence that bronchodilators should be delivered by VHC administering each puff separately and that the face mask should be omitted as soon as the child can hold the mouthpiece of the VHC tightly between the lips and teeth. VHCs should not be considered interchangeable when used with pMDI.⁴⁷

VHCs also reduce the need to coordinate breathing with actuation. They should be used with infants, small children, and any child receiving steroids because VHCs can reduce the pharyngeal dose of aerosol from the pMDI 10- to 15-fold compared with administration without a VHC. Berlinski et al. confirmed that most children with asthma, ages between 5 and 8 years, need three or fewer breaths to empty a small-volume VHC.⁴⁸

Dry Powder Inhalers

While DPIs offer several advantages, their use in children is often limited due to poor lung delivery efficiency and difficulties with consistent DPI usage. Therefore, DPIs are usually not appropriate for children younger than 5 years of age since these devices are driven by peak inspiratory flows much greater than those required by pMDIs.

Even if some young children can generate the 30 to 90 L/min range of inspiratory flow required by most inhaled corticosteroids (ICSs) to disperse adequate mass and particle size, it is questionable whether or not children can generate reproducible inspiratory flow patterns.⁴⁹ In addition, competence and good understanding in the child will be necessary to perform the steps required to take full advantage of the device. If, for example, a child exhales into a DPI, condensation will form inside the device and can prevent optimal dispersion of the powder into the mouthpiece.

Several technologies have recently been developed or progressed that can substantially improve the efficiency and reproducibility of DPI use in children as young as two years of age. These include nose-to-lung administration with small particles, active positive-pressure devices, structures to reduce turbulence and jet momentum, and highly dispersible excipient enhanced growth particle formulations.⁵⁰

Use of Selective Agents in Neonatal and Pediatric Patients

Although a wide variety of aerosol devices have been made available to deliver aerosol for therapeutic purposes, a very limited number of the newer drugs and those in development are approved by the FDA for use in the neonatal and pediatric populations. However,

research on pediatric and adult models has helped in clarifying the role of some novel therapies, which are summarized below.

Antibiotics

Aerosolization has been known to deliver a high concentration of antibiotic to the airway with minimal systemic absorption, side effects, and toxicity. The first commercially available antibiotic for aerosol administration was tobramycin solution for inhalation (or TOBI), approved for the therapy of cystic fibrosis (CF). Currently available FDA-approved aerosolized antibiotics include TOBI, aztreonam, and several antiviral agents. Colistin, although not FDA approved for inhalation, is commonly used off-label for nebulizing the IV solution form of the agent. Other antimicrobials being developed for aerosol use include quinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin and neomycin), and antifungal agents. These agents are designed to target pulmonary infections that include ventilator-associated pneumonia (VAP), tuberculosis, and seasonal influenza. The use of nebulized antibiotics in tracheotomized children has been recently associated with a reduction of the number of hospitalizations, length of stay in the intensive care unit, and bacterial load in with persistent airway colonization without significant side effects.⁵¹

Mucoactive Agents

These agents are designed to influence mucus secretion or mucus clearance. Dornase alfa is the only approved peptide mucolytic for the treatment of CF and has been available for more than a decade. Actin depolymerizers, such as thymosin agents and β -4, are synergistic with dornase alfa and appear not only to act as a mucolytic but may have antiinflammatory properties.⁵²

Expectorants and mucokinetics that have been evaluated in small children include hypertonic saline and dry powder mannitol. These medications act by increasing ion and water transport across the epithelium, altering the mucus rheology, inducing mucin secretion, and stimulating ciliary beating; more than simply acting as “airway hydrators.” The Australian National CF Hypertonic Saline study showed fewer pulmonary exacerbations and a significant improvement in FEV₁ in subjects with CF with use of hypertonic saline compared with normal saline.⁵³ Small studies have suggested that hypertonic saline may not be as effective as dornase alfa in improving FEV₁ in persons with CF.⁵⁴ Because hypertonic saline can irritate the airway and cause bronchospasm, it is usually administered along with a β_2 -adrenergic agent, such as albuterol. Inhaled dry powder mannitol has been shown to be effective in improving pulmonary function and reducing exacerbations in patients with CF and appears to be tolerated, at least as well as hypertonic saline.⁵⁵ A recent study found that in children with CF who tolerated long-term (12 months) treatment with DPI mannitol and dornase alfa made greater improvements in pulmonary function tests than treatment with dornase alfa alone.⁵⁶

The improvement in pulmonary function with mannitol appears to be sustained for at least 18 months.⁵⁷ Unfortunately, bronchoconstriction and cough have been largely responsible for the high attrition rate observed in a few clinical trials, and the improvement in pulmonary function does not appear superior to the administration of dornase alfa.^{58–60} Although the combination of inhaled mannitol and dornase alfa does not cause any additional improvement in pulmonary function in patients with CF, combining inhaled mannitol as a therapeutic carrier with bronchodilators and antibiotics may benefit patients with

pulmonary hypersecretion and infection.⁵⁷ Despite the positive results obtained with nebulized *N*-acetylcysteine in 100 children (ages 2–24 months) with acute bronchiolitis, the use of this agent is still controversial.^{61,62}

The most recent meta-analysis evaluating nebulized hypertonic saline concluded that it may modestly reduce length of stay among infants hospitalized with acute bronchiolitis and improve clinical severity score. Treatment with nebulized hypertonic saline may reduce the risk of hospitalization among outpatients and emergency department patients, and when incorporated to other airway clearance techniques, it can improve dynamic lung volumes and morbidity in children with non-CF bronchiectasis.⁶³

In a recent study, children with a confirmed diagnosis of asthma with mild or moderate asthma were randomized to receive a nebulization with 2.5 mg of albuterol diluted in 3 cc of hypertonic saline solution (3%) or normal saline solution (0.9%), by means of a jet nebulizer. They found that albuterol produced a greater bronchodilatory response when nebulized with 3%-HSS compared to NSS.⁶⁴

Aerosol Surfactants

Some of the neonatal and pediatric diseases that are characterized by surfactant inactivation include respiratory distress syndrome (RDS), CF, acute respiratory distress syndrome (ARDS), meconium aspiration, and severe asthma. Surfactant works as a mucokinetic or adhesive medication and may have antiinflammatory properties. Delivery of liquid surfactant in a nebulized form has been shown to be challenging because of its high viscosity and formation of foam at high-velocity airflows. In vitro and animal studies have suggested that surfactant and perfluorocarbons can be aerosolized using an inhalation catheter.^{65–67} Minimally Invasive Surfactant Therapy (MIST) via aerosolization is being actively pursued in research.^{68,69}

Degradation of airway surfactant in the CF airway can impair mucociliary clearance. Surfactant can reduce sputum stickiness, and the aerosolization of surfactant has been shown to improve pulmonary function in patients with chronic obstructive pulmonary disease (COPD). In addition, use of inhaled surfactants may improve antibiotic distribution within the lungs.⁷⁰

Antiinflammatory Drugs and Antibiotics

Although ICSs are the most used antiinflammatory medications for the treatment of asthma, several other drugs have been studied as aerosols in the pediatric population with CF. Recombinant secretory leukoprotease inhibitor, antineutrophil elastase, and α_1 antiproteases can decrease the activity of neutrophil elastase in the chronically inflamed airway. Aerosolized glutathione is currently being studied as adjuvant therapy for the treatment of CF.⁷¹

Cyclosporine analogs can be efficiently nebulized and may protect against the airway inflammation and allergic challenge present in patients with asthma. Aerosolized cyclosporine appears to ameliorate important pulmonary function parameters in lung transplant recipients compared with an aerosol placebo and historical control patients.⁷²

Patients with CF are known to be affected by recurrent bacterial infections. It is in this group of patients that most clinical trials have evaluated the use of nebulized antimicrobials. Dry powder tobramycin and colistin can be substituted for the same drug delivered by nebulization. Nebulized aztreonam needs more studies to determine its place.⁷³ In addition to tobramycin, colistin,

and aztreonam, levofloxacin has been approved in Europe to treat *Pseudomonas aeruginosa* infections. Nevertheless, no lung deposition data on inhaled levofloxacin are yet available.⁷⁴

Aerosolized Peptides and Proteins

Peptides have been delivered as aerosols both to treat pulmonary diseases, such as CF, and systemic diseases, such as diabetes. Particularly with CF, large peptides might include gene-transfer therapy, with use of complementary DNA delivered as an aerosol in a vector package to the affected cells.⁷⁵

Prostacyclin Analogs for Pulmonary Hypertension

The prostacyclin analogs epoprostenol and iloprost are well accepted as nebulized medications for treating severe pulmonary hypertension,⁷⁶ including in the setting of respiratory distress syndrome of the neonate and after surgery to correct congenital heart disease.^{77,78} Inhaled iloprost showed greater safety compared with the intravenous preparation, with preferential vasodilatation in the pulmonary circulation. A drawback of inhaled iloprost is the short hemodynamic effect, necessitating frequent administration of doses. Prostacyclin analogs with a longer half-life (e.g., treprostinil) and controlled-release formulations have been successfully evaluated with several aerosol delivery devices that include vibrating mesh nebulizers and the Tyvaso inhalation system, even for infants and children during high-frequency oscillatory ventilation.^{79–81}

KEY POINT

Aerosolized bronchodilators change respiratory mechanics in ventilated and nonventilated infants.

Adherence, Compliance, and Cooperation During Aerosol Therapy

Perhaps the largest challenge with drug delivery is related to behavioral and emotional aspects that are unique to pediatric patients. Infants and toddlers do not have the cognitive or physical abilities to coordinate their breathing efforts with the treatment.⁸²

With regard to adherence, defined as the process by which the patient strictly follows a regimen of care, greater than 60% is associated with a better level of asthma control.⁸³ The most reliable and accurate methods of evaluating adherence in children are the electronic and analog dose-counting monitors because their measurements are more reliable than reports by patients or family members, clinical judgment, drug dispensing by the pharmacy, and weighing of dose-counting inhalers.^{84–86}

However, the most important factor to consider in the administration of aerosol therapy in infants and young children is compliance. Two practical issues are important to consider when dealing with young children, particularly infants: facemask and crying. The interaction between crying and the facemask is complex. It is very likely that crying and distress, even with the best-designed facemask, result in poor seal, which seriously affects the efficiency of aerosol administration in young children. Calming the child and securing a tight face-to-mask seal is critical for successful drug delivery.

Facemasks Design, Fitting, Crying, and “Blow-By”

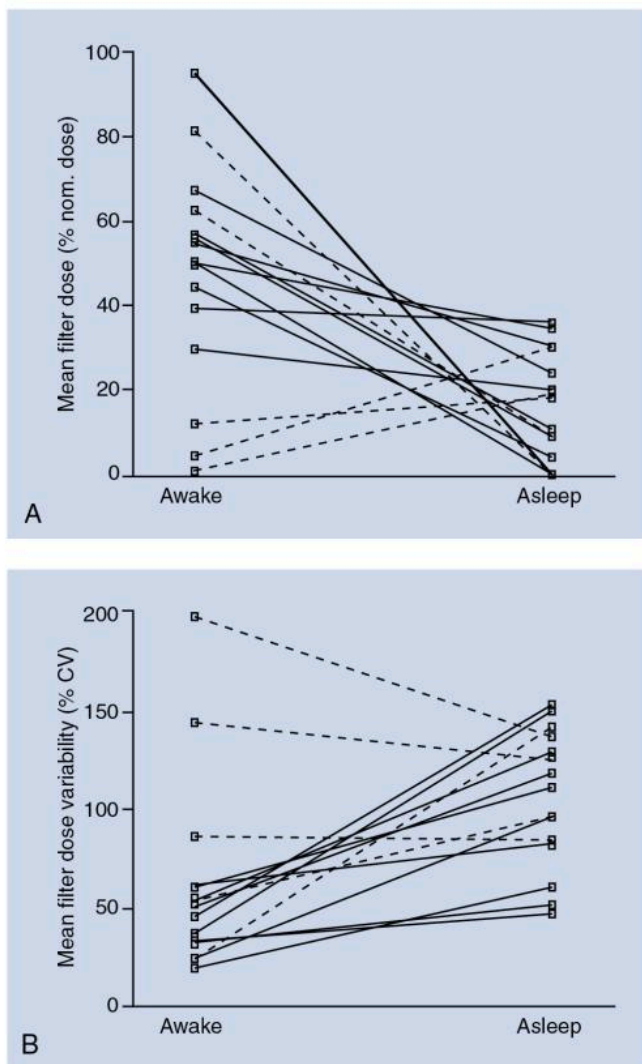
Aerosol delivery via a mouthpiece may provide twice as much drug compared with a facemask and is the most effective interface in spontaneously breathing older pediatric patients.²² However, most children must be about 3 years of age before they fully understand why and how a mask is used. It is important to select a lightweight and flexible facemask with anatomic contours and small dead space to increase the tolerability of the facemask during inhalation therapy in children. In neonates, the use of facemasks with less dead space is associated with greater inhaled dose, particularly when used with mesh nebulizers or pMDIs that do not add gas to the system during treatment.

Traditional facemasks designs can be divided into two categories: (1) front-loaded facemasks and (2) bottom-loaded facemasks. Front-loaded facemasks (Bubbles Fish II Mask, PARI, Midlothian, Virginia) have small entrainment ports on the side of the mask and direct aerosol toward the oronasal area of the patient. Bottom-loaded facemasks direct aerosol toward the upper part of the mask. Front-loaded facemasks appear to be associated with higher aerosol deposition and lower deposition in the eye and face compared with bottom-loaded facemask.

Keeping a good facemask seal during inhalation therapy is frequently associated with crying and rejection of the facemask. Previous research showed that aerosol drug delivery to children will decrease significantly without an optimal facemask seal because of leaks, crying, or intolerance of the facemask. Crying is associated with high inspiratory flows, high-dose variability, and almost no lung deposition.^{87,88} A typical pediatric patient does not tolerate a mask applied to the face, and agitation and crying are frequently observed. The efficacy of aerosol therapy administered to a combative or crying toddler is known to be negligible because of the changes in respiratory patterns during nebulization. Amirav et al. showed that the more the distress in infants during treatment, the higher the amount of aerosol deposited extrathoracically.³ This finding should alert clinicians to the potential for increased systemic absorption and a greater risk of side effects.

Although the poor aerosol delivery associated with crying could theoretically make aerosol administration during sleep an attractive alternative, the positive results of *in vitro* studies have not been consistently reported *in vivo*. Almost 70% of children wake up when aerosol is given during sleep and become distressed, resulting in similar lung deposition found with crying. However, a very recent study by Amirav et al. on 13 infants using the Soother-Mask revealed that all infants received the treatment during sleep without difficulty and that mean lung deposition averaged $1.6\% \pm 0.5\%$ in the lung.⁸⁹ Because crying may be inevitable, the caregiver may have to find creative ways to prepare the child for the facemask at a time when the child does not need the treatment.⁹⁰ This strategy would apply to maintenance therapy and not to the emergency setting or transport, where distracting and comforting the child may be the only available options to improve compliance. Dose variability seems to be independent of facemask design and more dependent on cooperation⁹¹ (Fig. 17.5).

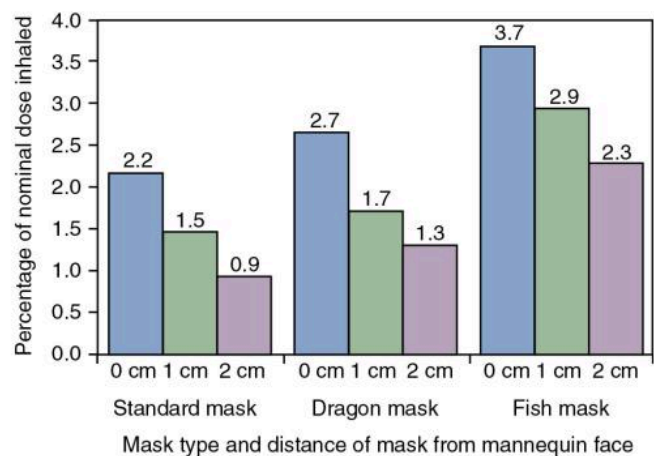
The absence of a tight seal between the mask and the patient's face results in a decrease in the amount of medication available for inhalation. Many parents are forced to hold the facemask near the face to avoid struggling with the child. This technique is commonly referred to as “blow-by.” However, it has been clearly documented in numerous studies that even a 0.5-cm gap in the facemask can drastically reduce the efficiency of drug delivery up to 50% in a lung model or spontaneously breathing children.⁹² In



• **Fig. 17.5** **A**, Mean filter dose, expressed as the percentage of the nominal (*nom*) dose, during awake administration and during sleep administration for children who slept through the administration procedure. **B**, Mean filter dose variability (%CV) during awake administration and during sleep administration for children who slept through the administration procedure. Straight line = Cooperative child; dotted line = uncooperative child during awake administration. (From Esposito Festen, J. E., Ijsselstijn, H., Hop, W. C. J., et al. [2006]. Aerosol therapy by pMDI-spacer in sleeping young children: to do or not to do? *Chest*, 130, 487–492.)

addition, “blow-by” cannot be used with pMDIs with VHCs and BANs because of poor mask seal, which will inhibit valve opening. In the case of mesh nebulizers, blow-by cannot be used because of lack of supplemental gas flow.^{14,93,94}

To evaluate the effect of mask-fit and crying on aerosol delivery, Erzinger et al.⁹⁵ studied eight children, ages 18 to 36 months, with recurrent wheezing for the administration of radiolabeled salbutamol with either a vent-assisted nebulizer or a pMDI attached to a holding chamber. Lung deposition expressed as a percentage of the total dose (metered dose and nebulizer fill, respectively) was 0.2% and 0.3% in children who inhaled via a facemask that is not tightly fitted. Lung deposition was 0.6% and 1.4% in screaming children with a tightly fitted facemask and between 4.8% and 8.2% in patients breathing normally. Overall mask deposition was between 0.8% and 5.2%. Overall face deposition was between 2.6% and 8.4%.⁹⁵



• **Fig. 17.6** Mean values of inhaled drug mass for all facemasks at varying distances from the inhalation filter. The differences between the Fish facemask and both the standard and the Dragon facemasks were significant at all distances. There was a significantly higher inhaled drug mass for all masks at 0 cm compared with 2 cm. $P < 0.001$, all masks compared at 0 cm versus 2 cm. $P < 0.001$, Fish facemask compared with standard and Dragon facemasks at all distances. (From Lin, H-L., Restrepo, R. D., & Gardenhire, D. S. [2005]. An in vitro investigation of nebulized albuterol delivery by pediatric aerosol facemasks to spontaneously breathing infants. *Respiratory Care*, 50, 1551.)

Development of more efficient, more acceptable, and friendlier facemask interfaces has been evaluated as an option to improve the inhaled drug mass. Reports comparing the standard aerosol pediatric mask with other proprietary masks have shown that the newly designed masks significantly increase the inhaled drug mass⁹⁶ (Fig. 17.6).

The first facemask interfaces had several shortcomings, most notably large dead space and chamber volumes, making it difficult for infants to clear with normal tidal breathing. Improvements were made in later devices by decreasing dead space, reducing electrostatic charge, and improving mask fit.⁹⁷ The SootherMask (InspiraRx, Somerset, New Jersey) is one of the newest devices and is designed for the facial structure of infants and children. It allows aerosol delivery during nasal breathing, so an infant can continue to use a preferred oral pacifier during treatments.⁹⁸ A scintigraphy study by Amirav et al. with this device showed that aerosol deposition in the lungs of infants was comparable with that via a standard nebulizer mask.⁹⁷ The mask is held in place mostly by the difference between atmospheric pressure and the infant's suction, so very little external pressure is needed. The InspiraMask (InspiraRx) is intended for older children and does not allow use of a pacifier. Both devices can be paired with either a VHC or a nebulizer. Despite the level of innovation behind these facemasks, it is recommended that children be switched to a mouthpiece as soon as they are old enough to inhale through the mouth voluntarily.

High-Flow Nasal Cannula

Nasal delivery of aerosolized medications to the lungs of children is superior or more effective compared with oral delivery.^{98,99} Because infants and young children are obligate nose breathers, administration of aerosol therapy through high-flow nasal cannula appears to be a logical approach to improve treatment outcomes.

The use of high-flow nasal cannula (HFNC) has been associated with higher aerosol delivery compared with bubble



• **Fig. 17.7** Infant oxygen hood nebulizer. (Courtesy Utah Medical Products, Inc., Midvale, Utah.)

continuous positive airway pressure (CPAP) and sigh intermittent positive airway pressure (SiPAP) mandatory ventilation.^{100–103} Benefits of trans-nasal aerosol delivery include increased comfort, ability to speak, eat, and drink for patients while meeting a range of oxygen requirements, particularly for those who need to inhale aerosolized medication for long periods. Aerosol administration via HFNC has been shown to be well tolerated by children and adults, with comparable or better delivery efficacy than other interfaces, ranging from 2% to 20%.¹⁰⁴ Skin irritation from canulas and accumulation of condensate need special consideration in small children.^{103,105}

Nebulizer Hood

Because it is very difficult to hold a mask snugly fitted to the face, particularly in infants, other alternatives have been explored. The nebulizer hood was designed as an attempt to develop more acceptable and patient-friendly interfaces, and appears to deliver much greater aerosol amounts than via a mask in vivo and in vitro.^{106,107} Hoods seem to reduce the likelihood of agitation and crying in infants, significantly because nothing comes in contact with their face (Fig. 17.7).^{106,107}

The hood is easy to operate and can be applied when infants are asleep. Both the hood and the facemask can deliver similar amounts of aerosol; however, parents show a preference for the hood over the facemask.^{108,109}

Parent Education on Inhalation Therapy

Parents are routinely faced with the challenge of learning, sometimes rather quickly, how to use a variety of devices when their children are diagnosed with a respiratory disease that requires the use of aerosolized medications. In the emergency department, children are typically treated with bronchodilators via facemasks. After going home, children may require the use of different interfaces and inhaled medications. However, inhaled medications are often prescribed without demonstrating to parents how inhalation therapy should be administered with each device and interface. Therefore, parents do not know how to use each interface and how to solve problems that may arise during aerosol drug delivery to children. Use of techniques such as “blow-by” results from parents reacting to their baby resisting the use of a facemask. Unless educated by a health care provider, they do not know that this technique will reduce the efficiency of therapy; some parents may force the baby to accept the facemask by holding it tightly on the baby’s face and believing that crying improves aerosol drug delivery to their

children. Poor response to inhalation therapy could be associated with poor administration of aerosolized medications or interfaces; health care providers often assume that parents are competent in the administration of any therapy to their children. Reinforcement of instructions, along with back demonstration, is key to ensuring proper administration of inhalation therapy to children.¹¹⁰

Aerosol Administration in Intubated Neonatal and Pediatric Patients

KEY POINT

Although several aerosolized drugs have been used in the treatment of neonatal respiratory illnesses, an optimal aerosol drug delivery system for mechanically ventilated infants still does not exist. Several variables, including particle size, aerosol flows, nebulizer choice, and placement of the aerosol generator, represent a significant challenge in this age group. For example, an externally powered nebulizer may interfere with patient-triggered modes of ventilation, may cause increases in airway pressures and unexpected positive end-expiratory pressure (PEEP), and may result in variable FiO_2 levels. Aerosol drug depositional loss occurs in the aerosol generator, interface device, and ventilation circuit including the endotracheal tube (ETT), which has an internal diameter (ID) of approximately 3 mm in ventilated newborn infants. Additional challenges to lung deposition of pharmaceutical aerosols in infants include low tidal volumes; short inhalation periods, which increase inertial effects; high breathing frequencies; and small inspiratory-to-expiratory (I:E) ratios.¹¹¹

Aerosol delivery seems to be less efficient in intubated pediatric patients than in spontaneously breathing patients.¹¹² Although delivery efficiency to the lungs of intubated infants with conventional jet nebulizers and MDIs is typically 1% or less, newer vibrating mesh and USNs have significantly increased lung delivery efficiency of aerosols for ventilated infants to a value of approximately 10%.¹¹³ Nebulizers producing aerosol particles with a mass median aerodynamic diameter (MMAD) of 0.5 to 3 μm are more likely to achieve greater deposition in the LRT of small children undergoing mechanical ventilation.

It is important to consider changes associated with the use of jet nebulizers inline on ventilated pediatric, particularly neonatal, patients because unexpected changes in volume and pressure may have deleterious effects. An externally powered nebulizer increases volume and pressure during volume-targeted ventilation, creates a bias flow in the ventilator circuit that may interfere with patient-triggered modes of ventilation, may result in increased airway pressure and unexpected positive end-expiratory pressure (PEEP), and may result in variable FiO_2 levels. Constant flow during expiration significantly limits the concentration of the inspired aerosol. Other nebulizer designs, such as vibrating mesh/membrane systems, do not require a gas source to operate and do not affect airway pressures during operation as usually seen with externally gas-powered nebulizers. No differences in lung dose/delivery efficiency have been found at different tidal volumes values for the jet nebulizer and the vibrating mesh nebulizer. In a study by Berlinski and Willis,¹¹⁴ the vibrating mesh nebulizer had higher lung dose/delivery efficiency compared with the jet nebulizer, only when placed before the Y-piece. Moving the nebulizers from before the Y-piece to the ventilator increased lung dose/delivery efficiency for all conditions tested except the vibrating mesh nebulizer at a tidal volume of 100 mL.¹¹⁴

If rapid respiratory rates are used, the ventilator duty cycle may be inadequate for the aerosol cloud to develop in the circuit and may seriously decrease aerosol deposition.

The respiratory clinician should also be aware that aerosol delivery may be less effective with manual ventilation versus mechanical ventilation. Placement of the aerosol delivery device in an intubated infant requires the clinician's attention. Although most studies show a slightly higher lung deposition with the pMDI when inserted between the Y-piece and the endotracheal tube, when an SVN is placed in the inspiratory limb away from the Y-piece, lung deposition also is very low.¹¹⁵ In pediatric patients, a pMDI and spacer with a one-way valve is associated with a significantly larger amount of inhaled

drug mass.¹¹⁶ No difference has been found between the findings from in vitro and in vivo studies. It has been suggested that the pMDI be actuated before inspiration to improve lung deposition.^{117,118}

Newer devices, such as inline low-volume DPIs, appear to produce an acceptable high-quality aerosol with only 10 mL of dispersion air per actuation and are easy to load and operate. This performance should enable application in high-flow and low-flow mechanical ventilation systems and high-efficiency lung delivery to both infants and children.^{119,120}

Summary

Efficient aerosol therapy in young children is a challenge. Although the advantages with inhaled drugs to treat pulmonary problems in neonates and pediatric patients support their use, consensus is lacking in determining a suitable dose for this population. More recent research suggests that age has a dose-regulating effect on the amount of aerosol drug reaching the lungs, with less drug reaching the lungs of younger subjects. Safety profile, therapeutic efficacy, and efficiency of routinely aerosolized medications delivered to infants and children need to be rigorously studied. In patients younger than 6 months of age, tidal volumes and inspiratory flow rates can reduce the amount of aerosol drug inhaled from nebulizers or pMDI and spacer devices. Even when the inhaled dose is the same for both pediatric and adult patients, data indicate that the lung dose decreases for younger patients. Neonatal and pediatric patients should be assessed for the adverse systemic effects associated with aerosol drug administration because of inefficient drug absorption from the lung and the presence of large extrathoracic deposition when masks are not tightly applied.

Neonates and very young pediatric patients show clinical response to aerosolized bronchodilator administration, but how to determine doses for aerosolized drugs delivered to neonatal and pediatric patients is not completely understood. Despite the differences in drug action between adults and children, the ability to control particle size by selecting the optimal aerosol delivery,

placement of the aerosol device, and understanding patterns of aerosol generation are the key elements to improve efficiency of aerosol administration. Identifying the ability of the patient, rather than a specific age, is also essential to selecting the most appropriate device in any population.¹²¹

It needs to be kept in mind that optimal aerosol administration requires matching patient characteristics with the aerosol delivery system. Infants and young children are a special group of patients with different anatomic, physiologic, and behavioral characteristics that dramatically affect the outcomes of pharmacotherapy. Physicians, respiratory therapists, and nurses need to know how to select the right aerosol delivery device appropriately for children of different ages. In infants and young children, lack of coordination, inadequate inspiratory flows, limited cooperation, and crying are factors that greatly affect the efficiency of aerosol therapy. Because of the seriousness of the treatment and the possible errors in the inhalation technique, it is recommended that caregiver knowledge be reassessed at each patient encounter and that instructions be written in a manner that the caregivers can understand them. The development of in vitro models that better replicate not only the anatomy but also realistic breathing patterns may allow for better prediction of in vivo lung deposition of aerosols in neonatal and pediatric patients.¹²² It could be more relevant clinically to evaluate the physiologic effect of a pharmacologic aerosol in children than to dwell on scant data on drug deposition.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. Can an aerosol formulation for oral inhalation be legally administered to neonates, infants, and pediatric patients?
2. Can an adrenergic bronchodilator, such as albuterol, reduce airway resistance when used in neonates?
3. According to the data reviewed in this chapter, does the adult dose of an aerosol drug need to be reduced for neonatal and pediatric patients based on weight?
4. What aerosol delivery devices could be used with a 2-year-old child?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 24-month-old boy, who was born premature at 27 weeks' gestation, is brought to the emergency department in respiratory distress. His medical history is significant for bronchopulmonary dysplasia. Vital signs are as follows: temperature 37.5°C, pulse 175 beats/min, respiratory rate 76 breaths/min, blood pressure 85/55 mm Hg, and saturation of peripheral oxygen (SpO₂) 85% on room air. The physical examination reveals the presence of intercostal retractions, increased anteroposterior diameter, nasal flaring, and bilateral diffuse expiratory wheezing. The patient is administered oxygen and admitted to the pediatric intensive care unit. The attending physician orders a 1.25-mg unit dose of albuterol via a small volume nebulizer. During administration of the aerosol, the patient's pulse rate increases to 220 beats/min, and he becomes cyanotic despite the use of oxygen to nebulize the drug. The patient is promptly intubated and mechanically ventilated. The patient receives albuterol throughout his hospital course and is discharged home 2 weeks later with a prescription for albuterol syrup.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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Critical Care, Cardiovascular, and Polysomnography Agents

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18

Skeletal Muscle Relaxants (Neuromuscular Blocking Agents)

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

Uses of Neuromuscular Blocking Agents

Physiology of the Neuromuscular Junction

Nondepolarizing Agents

Mechanism of Action

Pharmacokinetics of Nondepolarizing Agents

Metabolism

Adverse Effects

Cardiovascular Effects

Histamine Release

Inadequate Ventilation

Reversal of Nondepolarizing Blockade

Depolarizing Agents

Mechanism of Action

Metabolism

Reversal

Adverse Effects

Sensitivity to Succinylcholine

Neuromuscular Blocking Agents and Mechanical Ventilation

Precautions and Risks

Use of Sedation and Analgesia

Interactions With Neuromuscular Blocking Agents

Choice of Agents

Monitoring of Neuromuscular Blockade

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to skeletal muscle relaxants
2. Define neuromuscular blocking agents (NMBAs)
3. List the uses of NMBAs
4. Describe the physiology of the neuromuscular junction
5. Describe the makeup of nondepolarizing agents
6. Describe the makeup of depolarizing agents
7. Describe uses of NMBAs and mechanical ventilation
8. Identify methods of monitoring neuromuscular blockade

KEY TERMS AND DEFINITIONS

Acetylcholinesterase (AChE) Enzyme that breaks down the neurotransmitter acetylcholine (ACh) at the synaptic cleft so that the next nerve impulse can be transmitted across the synaptic gap.

Amnestic properties Having the ability to cause total or partial loss of memory.

Aspiration Accidental inhalation of food particles, fluids, or gastric contents into the lungs.

Fasciculation Involuntary contractions or twitching of groups of muscle fibers.

Myasthenia gravis Autoimmune neuromuscular disorder characterized by chronic fatigue and exhaustion of muscles.

Nerve cell (neuron) A basic functional unit of the nervous system that is specialized to transmit electrical nerve impulses and carry information from one part of the body to another. A neuron consists of a cell body, axons, and dendrites.

Neuromuscular blocking agents (NMBAs) Substances that interfere with the neural transmission between motor neurons and skeletal muscles.

Neurotransmitter Chemical that is released from a nerve ending to transmit an impulse from a nerve cell to another nerve, muscle, organ, or other tissue.

Nosocomial pneumonia Pneumonia that is acquired in a health care setting.

Sedation Production of a restful state of mind, particularly by the use of drugs that have a calming effect, relieving anxiety and tension.

Somatic motor neurons Part of the nervous system that controls muscles that are under voluntary control.

Status asthmaticus Exacerbation of asthma that does not respond to standard treatment.

Status epilepticus At least 30 minutes of continuous seizure activity without full recovery between seizures.

Neuromuscular blocking agents (NMBAs), also termed *paralytics* or *muscle relaxants*, are drugs that cause skeletal muscle weakness or paralysis, preventing movement. These agents produce this effect at the neuromuscular junction by interfering with the action of the neurotransmitter acetylcholine (ACh). NMBAs either depolarize the presynaptic and postsynaptic membrane receptors or compete with ACh for binding of the ACh receptors at the neuromuscular junction.

KEY POINT

Neuromuscular blocking agents (NMBAs) are used for inducing skeletal muscle paralysis in several clinical situations, including intubation, surgery, and facilitation of ventilation in certain critically ill patients.

NMBAs are divided into two types: depolarizing agents and nondepolarizing agents. Depolarizing agents bind to ACh receptors and cause a sustained postsynaptic membrane depolarization. By preventing repolarization of the nerve ending, the postsynaptic ending becomes refractory and unexcitable, resulting in flaccid muscles. At present, succinylcholine is the only available agent in this class. Nondepolarizing agents produce paralysis and muscle weakness by competing with ACh for binding at the ACh receptors. By preventing the binding of ACh, nondepolarizing agents block the depolarizing effects of ACh, thereby preventing muscle contraction.

KEY POINT

The two types of NMBAs are nondepolarizing and depolarizing NMBAs. Nondepolarizing agents, such as rocuronium, competitively block the cholinergic nicotinic receptor on the postsynaptic muscle fiber, preventing ACh from depolarizing the muscle fiber. Depolarizing agents, such as succinylcholine, act by first depolarizing the muscle fiber and then prolonging the depolarized state to prevent repolarization and further stimulation.

Uses of Neuromuscular Blocking Agents

The clinical uses of NMBAs are as follows:

- To facilitate endotracheal intubation
- To obtain muscle relaxation during surgery, particularly of the thorax and abdomen
- To enhance patient–ventilator synchrony
- To reduce intracranial pressure (ICP) in intubated patients with uncontrolled ICP
- To reduce oxygen consumption
- To terminate convulsive **status epilepticus** and tetanus refractory to other therapies
- To facilitate procedures or diagnostic studies
- To paralyze selected patients who must remain immobile (e.g., trauma patients)

NMBAs are usually given intravenously and exhibit a dose-related response on muscles. The primary use of NMBAs in the operating room is for anesthesia induction before endotracheal intubation. In the intensive care unit (ICU), NMBAs are used primarily for management of mechanical ventilation.

CLINICAL CONNECTION

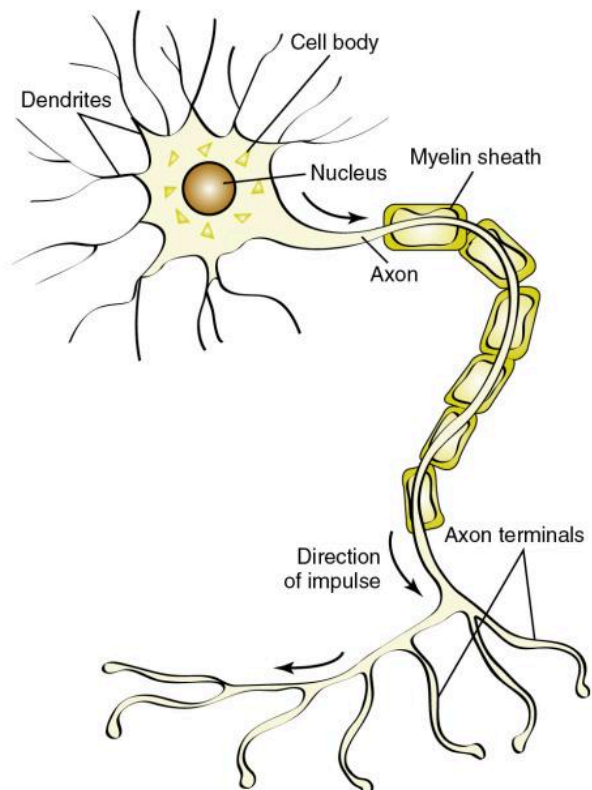
The most common examples of ventilated patients requiring muscle relaxation are patients with severe asthma, reduction of oxygen consumption in patients with difficult-to-manage conditions, such as acute respiratory distress syndrome (ARDS), and patients requiring “uncomfortable” modes of ventilation, such as pressure-controlled inverse ratio ventilation.

Physiology of the Neuromuscular Junction

The autonomic nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord, and the PNS includes all the nerves outside of the CNS. The PNS is divided further into the **somatic motor neurons**, sensory afferent neurons, and autonomic motor neurons. The somatic motor neurons include all the peripheral nerves that control skeletal muscle over which humans have control of “voluntary” movement. Examples of skeletal muscles include the quadriceps, biceps, diaphragm, and accessory muscles of ventilation, which are responsible for motor functions, such as movement, lifting, and breathing. The autonomic motor neurons include peripheral nerves that control smooth muscle (e.g., wall of the digestive system, vascular smooth muscle), cardiac muscle (rate and force of contraction), and glands (e.g., adrenal medulla, sweat glands, exocrine glands of the pancreas). For a review, refer to [Chapter 5](#).

The basic **nerve cell**, or **neuron**, consists of a *cell body*, *axons*, and *dendrites* ([Fig. 18.1](#)). The cell bodies of somatic motor neurons, which are located in the spinal cord, stimulate skeletal muscles via the axons running through the peripheral nerves. These axons are large myelinated nerve fibers extending from the peripheral nerve cell bodies to the muscle fibers. A single peripheral nerve branches and innervates many different muscle fibers as a *motor unit*. The area between the nerve and muscle, or *synapse*, is specialized into a *motor end plate*. This area between the axon and the skeletal muscle fiber is also termed the *neuromuscular junction* ([Fig. 18.2](#)).

The transmission of nerve signals in the skeletal muscle is chemically mediated by the **neurotransmitter** ACh. When a nerve impulse reaches the end of the motor neuron, ACh is released from the presynaptic membrane into the synaptic cleft. ACh diffuses

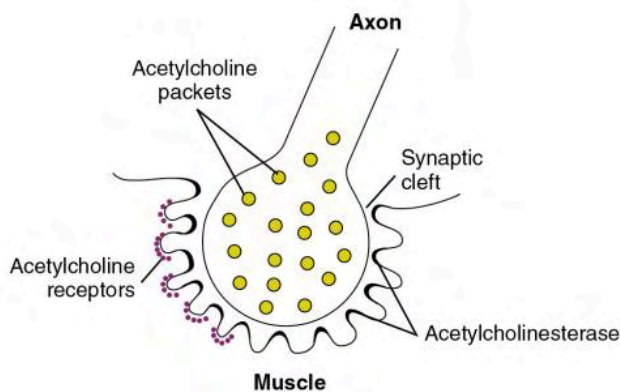


• **Fig. 18.1** Schematic drawing of a nerve cell.

across the synaptic space and interacts with specific Ach receptors on the postsynaptic muscle fiber membrane, resulting in a contractile response by the muscle fiber. During the short period that Ach is in contact with the receptor on the postsynaptic (muscle fiber) membrane, a nerve action potential, or nerve impulse, is initiated in the postsynaptic membrane. Ach is broken down and inactivated by the enzyme **acetylcholinesterase (AChE)**, allowing the muscle fiber to repolarize.

On the basis of the neuromuscular physiology described, muscle contraction may be blocked in the following two ways:

1. **Competitive inhibition:** The binding and blocking of the Ach receptors without depolarization; this is the action of the *nondepolarizing* agents.



• **Fig. 18.2** Schematic description of the anatomy of the motor end plate.

2. **Prolonged occupation and persistent binding of the Ach receptors:** Resulting in sustained depolarization of the neuromuscular junction; this is the action of the *depolarizing* agents.

Both depolarizing and nondepolarizing agents resemble the neurotransmitter Ach. **Table 18.1** reviews both types of NMBA, including major chemical classification, duration of action, and elimination route.

Nondepolarizing Agents

The earliest groups of NMBAs used clinically were agents, such as curare. These agents paralyze skeletal muscle by simple competitive inhibition of Ach at muscle receptor sites. This group is referred to as *nondepolarizing* because they block the Ach receptors without activating them. Chemically, nondepolarizing NMBAs are steroid-structured agents (vecuronium, rocuronium, and pancuronium), Bisbenzyltetrahydroisoquinoline agent (mivacurium), or benzyloquinoline esters (atracurium and cisatracurium). The differences among the structures are important with regard to complications and side effects.

Mechanism of Action

Nondepolarizing agents cause muscle paralysis by affecting the postsynaptic cholinergic receptors at the neuromuscular junction. By either blocking the channel externally, occupying the channel pore, or affecting the receptor from the internal side of the muscle membrane, these agents reduce the frequency of channel opening. Nondepolarizing agents compete against endogenous Ach for receptor occupancy. Muscle contraction does not occur if enough sites are

TABLE 18.1 Classification of Neuromuscular Blocking Agents (NMBAs)

Agent	Chemical Class	Pharmacologic Properties	Time of Onset (Min)	Clinical Duration (Min)	Mode of Elimination
Depolarizing NMBAs					
Succinylcholine (Anectine, Quelicin)	Dicholine ester	Ultrashort duration	1–1.5	10–15	Hydrolysis by plasma cholinesterases
Nondepolarizing NMBAs					
Atracurium	Benzyloquinoline ester	Intermediate duration; competitive	2–4	30–60	Hofmann degradation; hydrolysis by plasma esterases; renal elimination
Cisatracurium (Nimbex)	Benzyloquinoline ester	Intermediate duration; competitive	2–3	40–60	Hofmann degradation; hydrolysis by plasma esterases; renal elimination
Mivacurium (Mivacron)	Bisbenzyltetrahydroisoquinoline	Short duration; competitive	2–3	20–30	Hydrolysis by plasma cholinesterases
Pancuronium	Ammonio steroid	Long duration; competitive	4–6	120–180	Renal elimination
Rocuronium	Ammonio steroid	Intermediate duration; competitive	1–2	30–60	Liver metabolism
Vecuronium	Ammonio steroid	Intermediate duration; competitive	2–4	60–90	Liver metabolism and clearance; renal elimination

blocked by these agents. This is illustrated in Fig. 18.3, which shows that the drug (ND) occupies and then blocks the postsynaptic site at the neuromuscular junction. With nondepolarizing agents, depolarization of the postsynaptic membrane becomes a function of the amount of drug and the amount of Ach located around the receptor. In other words, because nondepolarizing agents act by competitive inhibition, their effect is dose related: larger doses overcome the effects of Ach and block more receptors. The receptor blockade by nondepolarizing agents can be reversed by making more Ach available to compete for receptor sites. Inhibitors of AchE, an enzyme that breaks down Ach, can be used to reverse the competitive blockade. Neostigmine is an example of a cholinesterase inhibitor.

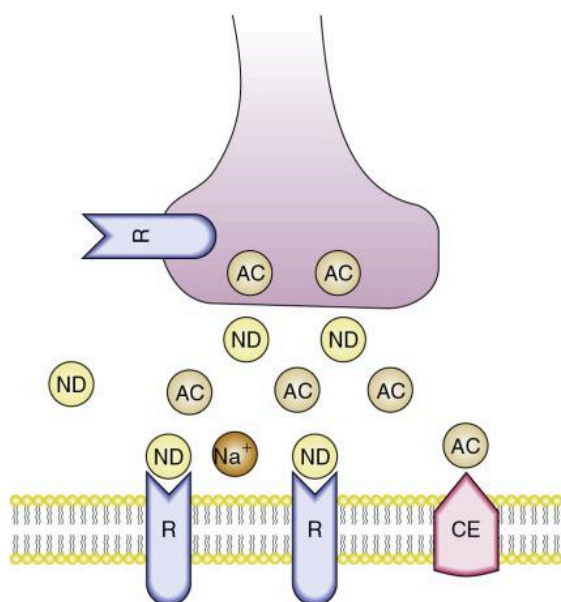
Pharmacokinetics of Nondepolarizing Agents

Nondepolarizing NMBA chemically resemble Ach. These agents have a positively charged quaternary ammonium group (NH_4^+) that binds to the negatively charged Ach receptor. Nondepolarizing agents are poorly lipophilic and do not penetrate well into fat tissue or across the blood–brain barrier. Also, these agents are poorly absorbed from the gastrointestinal tract and therefore must be given intravenously to allow rapid onset of neuromuscular blockade.

The onset of paralysis and the duration of action of nondepolarizing blockers vary widely among members of this group of drugs. Pancuronium has the longest duration of action and is considered a long-acting NMBA. Atracurium, cisatracurium, vecuronium, and rocuronium are redistributed more rapidly and have shorter durations of action. These agents are considered intermediate-acting NMBA.¹ Of all the nondepolarizing agents, mivacurium has the shortest action.²

KEY POINT

Nondepolarizing agents usually have a longer duration of action compared with the depolarizing agent succinylcholine.



• **Fig. 18.3** Competitive blocking agents, or nondepolarizers (ND), occupy but do not activate acetylcholine receptors (R). Acetylcholine (AC) is prevented from occupying receptors and muscle contraction fails to occur. Released acetylcholine is rapidly metabolized by membrane cholinesterase (CE). Nondepolarizers can also bind to prejuncional acetylcholine receptors and modify acetylcholine release. Na^+ , Sodium.

As previously noted, the magnitude of effect, rate of onset of maximum blockade, and duration of action of NMBA are dose dependent; these are listed in Table 18.2 for the drug rocuronium when used in adults. Factors such as advanced age generally increase the length of neuromuscular blockade activity. Hepatic or renal failure can cause decreased clearance, increased blood levels, and prolonged duration of action for agents metabolized and eliminated by the liver and the kidneys.

Metabolism

Neuromuscular blockade diminishes and transmission is restored after a single bolus dose once the agent is cleared off the receptor site via redistribution to the rest of the body. When normal conduction returns, 75% of Ach receptors may still be occupied by a blocker; this explains why additional boluses of NMBA seem more potent and have a markedly prolonged duration of action. After prolonged infusion or repeated boluses, metabolism and excretion provide the mechanism for removal of the blocking agent from the neuromuscular junction.

Pancuronium is eliminated primarily by the kidneys. Pancuronium also undergoes some hepatic metabolism with production of an active metabolite that is eliminated by the kidneys.

Alternatively, vecuronium is an agent metabolized primarily by the liver. The metabolite of vecuronium also has activity and relies on the kidneys for excretion. All of these agents can accumulate in renal failure and cause prolonged paralysis when given in sufficient doses.

Atracurium and cisatracurium differ from other NMBA with regard to the route of elimination. These agents are partly inactivated by a spontaneous degradation mechanism that is dependent on the pH of blood and temperature of the body. This nonenzymatic breakdown is termed *Hofmann degradation*. In addition to Hofmann degradation, these agents are rapidly converted to less active metabolites by circulating plasma esterases that cause hydrolysis of the compounds. Because of the lack of liver and kidney elimination, atracurium and cisatracurium are optimal choices for patients with hepatic or renal failure.

Atracurium further differs from cisatracurium because it has a breakdown product of Hofmann degradation called *laudanosine*. Laudanosine, which is eliminated primarily by the kidneys and is slowly metabolized by the liver, has a long half-life and can cross the blood–brain barrier. Laudanosine has been associated with neurostimulatory effects. CNS excitation and seizures should be considered as a possible complication, especially in patients receiving atracurium who have impaired renal function or liver failure.³ Cisatracurium has less laudanosine production compared

TABLE 18.2 Dose-Dependent Effects of Rocuronium in Adults

Dose (mg/kg)	Time to Maximum Block (Min)	Clinical Duration (Min)
0.45	3	22
0.6	1.8	31
0.9	1.4	58
1.2	1	67

Data from *Drug Facts and Comparisons*. (2018). St. Louis, Missouri: Wolters Kluwer Health.

TABLE 18.3 Comparison of Side Effects of Neuromuscular Blocking Agents

Agent	Histamine Release	Blockade of Autonomic Ganglia	Blockade of Vagal Response	Vagal Stimulation
Atracurium	++	0	0	0
Cisatracurium	+	0	0	0
Mivacurium	+	0	0	0
Pancuronium	+	++	++	0
Rocuronium	+	0	+	0
Succinylcholine	+	0	0	+++
Vecuronium	0	0	0	0

0, No effect; + through +++, degree of effect.

with atracurium and is considered more potent. The risk of further brain injury from seizures in patients with poor intracranial compliance (e.g., severe head injury) may make these drugs poor choices in these patients.⁴ These agents, which complicate assessment of the patient, might mask seizure activity. Mivacurium is a mixture of three isomers and has the shortest duration. The agent is metabolized by plasma cholinesterase and eliminated in urine.²

Adverse Effects

Cardiovascular Effects

It is important to understand that the nondepolarizing NMBA also competitively block Ach receptors at the autonomic ganglia, producing cardiovascular side effects on heart rate and blood pressure. They may cause a vagolytic effect, which produces tachycardia, and an increase in mean arterial pressure by promoting an increase in norepinephrine, a potent vasoconstrictor.⁴ Pancuronium has the greatest potential to cause cardiovascular side effects, especially tachycardia and hypertension. Vecuronium and cisatracurium have minimal effects on heart rate and blood pressure.

Histamine Release

All of the nondepolarizing agents have a tendency to release histamine from mast cells. However, the potential for adverse cardiac effects varies among the different agents. Clinically, histamine release can cause hypotension secondary to direct vasodilation, reflex tachycardia, and bronchospasm, leading to increased airway resistance. The vasodilatory effect may also give the appearance of skin flushing. The degree of histamine release for several NMBA is shown in Table 18.3. Atracurium has been reported to stimulate the most histamine release, which could cause bronchoconstriction. It is recommended that this agent be given at a reduced rate or at lower doses to avoid these effects. Antihistamines may also be administered as pretreatment to avoid such effects.

Inadequate Ventilation

Muscle paralysis of the diaphragm and the intercostals results in an inadequate respiratory function. Adequate airway control and ventilatory support are required until muscle recovery is adequate for spontaneous ventilation. Close patient and machine

monitoring are essential in the ICU to prevent hypoventilation and hypoxemia.

Reversal of Nondepolarizing Blockade

Muscle paralysis caused by nondepolarizing NMBA can be reversed by use of cholinesterase inhibitors, such as neostigmine. Neostigmine inhibits cholinesterase, which would normally break down Ach. This action allows for more Ach to be available at the neuromuscular junction to compete with and displace the blocker from receptor sites. Other cholinesterase inhibitors include edrophonium and pyridostigmine. Edrophonium is rapid acting but also has the shortest duration of action. Pyridostigmine has a slower onset and is the longest acting; it is often used to treat **myasthenia gravis** and can be given orally.

Sugammadex (Bridion) involves the actual inactivation and removal of the NMBA from the neuromuscular junction and the body. Sugammadex functions by encapsulating the NMBA to form a complex that can no longer bind to the receptors. The kidneys excrete the stable complex that is formed. Sugammadex has been shown to reverse only rocuronium and vecuronium effectively. Adverse effects are mild and include nausea, dry mouth, cough, and taste perversions.⁵ Table 18.4 summarizes these agents with recommended doses to reverse neuromuscular blockage produced by the nondepolarizing agents.⁶

CLINICAL CONNECTION

The effects of nondepolarizing agents can be reversed with an indirect-acting cholinergic agent (cholinesterase inhibitor), such as neostigmine or sugammadex, a modified gamma cyclodextrin. There is no reversal agent for succinylcholine.

Because the reversing agents increase the levels of Ach, they also increase the effects of Ach at parasympathetic ganglia, producing cholinergic autonomic side effects. Major side effects of these agents include severe bradycardia and salivation. To reduce these adverse effects, such agents as atropine or glycopyrrolate are also given in conjunction with cholinesterase inhibitors. As vagolytic and anticholinergic agents, atropine and glycopyrrolate, respectively, prevent bradycardia, increased salivation, and hyperperistalsis associated with excessive Ach.⁷

TABLE 18.4 Agents Used for Reversal and Antimuscarinic Effects With Nondepolarizing Blocking Agents

Agent	Dose (mg/kg)	Time to Effect
Reversal Agents		
Neostigmine	0.01–0.035	Intermediate onset and duration
Pyridostigmine	0.1–0.25	Slowest onset, longest acting
Sugammadex	2–4	Rapid onset, long acting
Antimuscarinic Agents		
Atropine	0.008–0.018	Rapid onset, short acting
Glycopyrrolate	0.002–0.016	Rapid onset, short acting

KEY POINT

Myasthenia gravis is caused by an immune response to acetylcholine receptors (AChRs), which are found on nerve and muscle cells. In this disease, the body produces antibodies that attack AChRs, preventing signals from reaching the muscles.

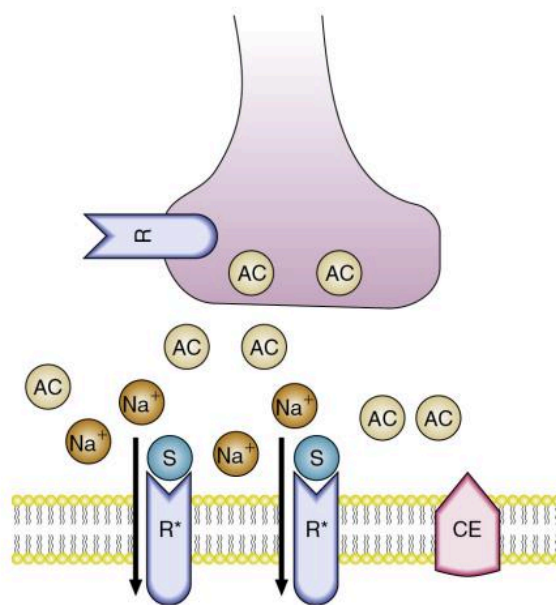
Depolarizing Agents**CLINICAL CONNECTION**

Succinylcholine has an ultrashort duration and is therefore used for intubation.

Depolarizing agents have a different mechanism of action from nondepolarizing agents; they are shorter acting, and there are no agents that reliably reverse their blockades. Succinylcholine is the only available agent in this group. An intravenous dose of 1 to 1.5 mg/kg causes total muscle paralysis in 60 to 90 seconds that lasts 10 to 15 minutes. Because of the quick onset and brief duration of action of succinylcholine, it is an ideal agent for patients requiring intubation.

Mechanism of Action

The initial action of depolarizing NMBA is to open sodium channels and depolarize the postsynaptic muscle membrane in the same manner as Ach. Depolarizing agents are resistant to the effects of AchE, allowing a persistent and longer duration of action at the neuromuscular junction. Because depolarization lasts longer, the membrane is unable to repolarize, resulting in flaccid muscles.⁷ This is illustrated in Fig. 18.4, which shows that molecules of succinylcholine (S) have occupied two Ach receptors, each opening a pore and allowing the local membrane to become permeable to sodium. If enough receptors are activated, depolarization occurs and is maintained until succinylcholine leaves the receptors. Further stimulation and contraction of the muscle fiber is impossible until the drug is removed by redistribution and metabolism.



• **Fig. 18.4** Succinylcholine produces a depolarizing block. Molecules of succinylcholine (S) occupy and activate the acetylcholine receptors (R^*), permitting sodium entry and an initial action potential. Continued occupancy prevents repolarization and the next action potential from released acetylcholine (AC). Activation of prejuncional acetylcholine receptors can modify acetylcholine release. CE, Cholinesterase; Na^+ , sodium; R, prejuncional receptor.

In contrast to any agent discussed so far, succinylcholine has a unique feature of blockade activity. On initial bolus dose, succinylcholine depolarizes the membrane, similar to Ach. The initial depolarization causes uncoordinated skeletal muscle contractions, referred to as **fasciculation**. Because succinylcholine remains at the neuromuscular junction longer than Ach, depolarization is prolonged, and flaccid paralysis occurs. This is referred to as *phase I block*. After prolonged use or large doses of succinylcholine, the type of blocking activity changes. Instead of showing depolarization characteristics, activity resembles the block produced by the nondepolarizing agents. This is referred to as *phase II block* or *desensitization block*. Phase II block involves a “fading” phenomenon in which stimulation of the motor neuron is poorly sustained and paralysis is prolonged. Although cholinesterase inhibitors can reverse phase II block, they may decrease the clearance of succinylcholine and enhance further blockade. The occurrence of a desensitization block must be considered as a possibility in patients with prolonged paralysis after succinylcholine administration. The fear of this “dual” mechanism limits the use of succinylcholine in repeated doses or as a continuous infusion.

Metabolism

Succinylcholine has a very short duration of action; this is mostly caused by its rapid hydrolysis by plasma cholinesterase in blood. Succinylcholine is metabolized to succinylmonocholine, which provides weak nondepolarizing activity. Succinylmonocholine is thought to account for some of the reason why repeated doses of succinylcholine produce prolonged blockade.

Reversal

No agents are available for the reversal of succinylcholine. Use of cholinesterase inhibitors, such as neostigmine, may delay the

elimination of succinylcholine, resulting in an even more prolonged depolarization and slower recovery of muscle activity.

Adverse Effects

Succinylcholine produces many side effects, several of which can be life threatening. The significance of these side effects may be of more concern in the ICU than during routine operating room use. Most adult patients have a sympathomimetic response causing tachycardia and an increase in blood pressure. Repeated bolus doses of succinylcholine may produce vagal responses, including bradycardia and hypotension. This side effect is seen more often in children. Succinylcholine also provokes histamine release, resulting in bronchospasm and hypotension in susceptible individuals.⁷

Muscle pain and soreness similar to myalgias are common after the administration of succinylcholine. A relationship between the pain and muscle fasciculations has been implicated but not confirmed. Some practitioners administer a small dose of a nondepolarizing blocker (e.g., 10% of the intubating dose) before giving succinylcholine to reduce fasciculations and pain.⁸ This pretreatment is often referred to as *defasciculation*. In patients receiving a nondepolarizing agent to prevent fasciculations, higher doses of succinylcholine are needed for complete paralysis because pretreatment reduces the effectiveness of succinylcholine. This practice is considered controversial because increased doses of succinylcholine are required, and pretreatment may cause partial paralysis, necessitating urgent intubation under nonideal conditions.² Muscle fasciculations can also cause an increase in serum potassium and creatinine phosphokinase, an effect that is also reduced but not totally eliminated by pretreatment.

Succinylcholine can cause an efflux of potassium from muscle cells, causing serum potassium to increase by 0.5 to 1 mEq/L in normal individuals.⁸ Patients with spinal cord injury or upper motor neuron lesions, thermal injuries, and severe trauma, including closed head injury, are at a higher risk of developing life-threatening hyperkalemia if succinylcholine is administered. Effects of severe hyperkalemia include arrhythmias and cardiac arrest.

Succinylcholine-induced fasciculations can increase intraocular pressure and intragastric pressure. Patients are at risk of extrusion of intraocular contents and aspiration of gastric contents. These conditions may be partially prevented by defasciculation.

Succinylcholine can dangerously increase intracranial pressure in patients with cerebral edema and head trauma by a mechanism that is not well understood.⁸ One of the most serious complications that can occur with succinylcholine is malignant hyperthermia. Malignant hyperthermia is caused by a genetic defect of muscle metabolism. It is a potentially fatal hypermetabolic state of skeletal muscles. An uncontrolled release of calcium from the sarcoplasmic reticulum of muscles occurs, resulting in a host of harmful effects. The clinical features can manifest as intractable spasm of the jaw muscles, rigidity, increased oxygen demand, severe hyperthermia, metabolic acidosis, and tachycardia. Malignant hyperthermia is treated with dantrolene, an agent that blocks the release of intracellular calcium from the sarcoplasmic reticulum. Early recognition and treatment are key to ensuring a full recovery.⁹

Sensitivity to Succinylcholine

As mentioned, succinylcholine is metabolized by plasma cholinesterase, which is also called *pseudocholinesterase*. In patients with abnormal or deficient pseudocholinesterase, succinylcholine is not metabolized effectively, and their recovery from paralysis is

prolonged. In these patients, long-term mechanical ventilation support is warranted. A family history of prolonged paralysis after surgery may suggest an abnormality in the enzyme. Laboratory tests are also available to determine the existence of abnormal cholinesterase.²

Neuromuscular Blocking Agents and Mechanical Ventilation

An indication for use of NMBA in patients receiving mechanical ventilation is to improve ventilator–patient synchrony. Ventilator dyssynchrony can cause increased intrathoracic pressure, decreased alveolar ventilation, and increased work of breathing for the patient. The desired goal with these drugs is to improve ventilation and oxygenation and to reduce ventilation pressures. Disease states in which neuromuscular blockade may be beneficial include the following:

- Acute respiratory distress syndrome
- Status asthmaticus, severe bronchospasm
- Certain modes of ventilatory support (e.g., pressure-controlled inverse ratio ventilation, high-frequency oscillatory ventilation)
- Status epilepticus or other intractable convulsive activity
- Neuromuscular toxins (e.g., strychnine poisoning)
- Tetanus

Patients with **status asthmaticus** and those with ARDS requiring pressure-controlled ventilation with or without inverse ratio ventilation to limit peak airway pressure are at highest risk of ventilator dyssynchrony.

Precautions and Risks

All patients receiving NMBA should receive additional care measures to decrease the negative effects that can be associated with the use of these agents. Proper eye care should be a standard of care for all patients receiving NMBA. Normally, eye blinking lubricates and cleans the corneas. NMBA cause paralysis of the eyelid muscles, which can result in corneal drying and ulceration. Appropriate eye lubrication and light taping of the eyes can prevent corneal abrasions. Eyes should be checked frequently.

With complete paralysis, the cough reflex is inhibited. Frequent suctioning along with appropriate sedation and analgesia to prevent pain and discomfort during suctioning is necessary. Retention of secretions is thought to increase the incidence of **nosocomial pneumonia** in patients receiving neuromuscular blockade for a prolonged period. Elevating the head can reduce the risk of **aspiration**, which is a risk factor for ventilator-associated pneumonia (VAP).

Support equipment must be closely monitored, including constant observation for extubation and ventilator malfunction. Alarm systems to detect hypoventilation and hypoxemia are the standard of care when NMBA are used.

Patients receiving prolonged therapy with NMBA are at risk for developing prolonged skeletal muscle weakness that persists long after the NMBA is discontinued. Myopathy, which may take months to resolve, may be associated more often with steroid-structured agents, such as vecuronium and pancuronium (see [Table 18.1](#) for classification), especially when they are combined with corticosteroids, such as prednisone. Daily physical therapy with range-of-motion exercises may lessen the potential for muscle atrophy or wasting in patients receiving prolonged NMBA therapy. Patients given an NMBA should also be turned frequently to

prevent the formation of pressure sores and decubitus ulcers. The risk of developing a deep vein thrombosis (DVT) is increased in these patients because of their immobility, making DVT prophylaxis imperative.

Use of Sedation and Analgesia

Of all adjunctive therapies patients may receive, it is essential to provide adequate **sedation** and analgesia for ventilated patients receiving a blocking agent. NMBA cause muscle paralysis without affecting consciousness or the perception of pain. In 1947, a classic experiment that established this fact was performed by Smith et al.,¹⁰ in which Smith allowed himself to be paralyzed with tubocurarine, an NMBA that is no longer marketed in the United States. He reported full awareness during the paralysis, including sensations of choking while he was unable to swallow as well as shortness of breath, even though he was being adequately ventilated. Neuromuscular blockade is unthinkable without proper sedation and pain control to prevent the nightmare of paralysis with full consciousness and sensory perception. Although many sedative and analgesic agents can cause hemodynamic instability, it is inappropriate to reduce or discontinue sedation and analgesia, while a patient is paralyzed, to address hemodynamic instability. Because clinical signs of restlessness, distress, and anxiety are lost with neuromuscular blockade, continuous cardiac monitoring is necessary, and vital signs should be assessed closely. Tachycardia, hypertension, diaphoresis, and lacrimation are physiologic responses that can indicate anxiety caused by inadequate sedation or lack of pain control.

KEY POINT

Paralysis in a conscious patient can be traumatic, so adequate sedation and analgesia are mandatory.

For short procedures, including endotracheal intubation, a sedative that has **amnestic properties** should be administered. In surgery, a sedative and an analgesic agent are recommended for all patients. For patients in the ICU, a sedative should be administered on a continuous basis before initiation of neuromuscular blockade. Continuous analgesia should also be used secondary to poor capacity for endurance of pain and the discomfort associated with the constant suctioning and the endotracheal tube itself. Sedatives that have amnestic effects include propofol, lorazepam, and midazolam. It is important to realize that these agents do not provide pain control. Analgesics commonly used for pain control include fentanyl, hydromorphone, and morphine. In many situations, deep sedation with continuously infused sedatives and analgesics may prevent the need for a blocking agent in the ICU. Other suggestions for sedation and analgesia are presented in [Chapter 20](#).

Interactions With Neuromuscular Blocking Agents

Several clinical conditions and medications may alter the effect of an administered NMBA. Because different blocking drugs may act at different locations on the Ach receptor–pore complex (e.g., external, in the pore, intercellular), combination with certain agents may be synergistic and potentiate blockade. Advantage has been taken of this potential to produce a combination of relaxant drugs that gives adequate relaxation with fewer cardiovascular side effects. Examples include combining inhaled anesthetics,

such as halothane or isoflurane, with a nondepolarizing NMBA. The inhaled anesthetics decrease the sensitivity of the neuromuscular junction to Ach, potentiating blockade. The dosage of the NMBA can be reduced, and this may decrease the side effects. The problem with this approach has been the unpredictability of the duration of relaxation, which tends to be extremely prolonged, especially after repeated mixture administrations.

Some classes of drugs and other conditions have neuromuscular blocking effects themselves; these may be additive, antagonistic, or synergistic with NMBAs. Aminoglycoside antibiotics are often administered to critically ill patients in the ICU. Aminoglycosides produce blockade by inhibiting the release of Ach from presynaptic nerve endings and, to a lesser extent, by blocking the postsynaptic receptor. Agents such as phenytoin, azathioprine, and theophylline antagonize neuromuscular blockade.

Clinical factors, such as acidosis, hypokalemia, hyponatremia, hypocalcemia, and hypermagnesemia, all potentiate neuromuscular blockade. Alkalosis and hypercalcemia are known to inhibit the effects of blockade. Factors affecting the activity of NMBAs are listed in [Table 18.5](#).

Choice of Agents

Characteristics of the perfect NMBA (not yet developed) include the following:

- Nondepolarizing block
- Rapid onset of action
- Predictable and controllable duration of action
- Hemodynamic stability at all levels of block and rate of administration
- No histamine release
- Predictable kinetics independent of age, sex, and organ dysfunction
- No active metabolites or toxicity
- Inexpensive

To date, there is no NMBA that exhibits all these ideal characteristics. Selection of an appropriate NMBA depends on the situation. Several factors must be taken into account when choosing an agent, including duration of procedure (consider duration of action), the need for quick endotracheal intubation (consider onset of action), adverse-effect profile (hemodynamic stability, histamine release), route of elimination (especially in patients with renal or hepatic insufficiency), concurrent medications and other drug interactions, and cost. The depolarizing agent succinylcholine is well suited only for intubation because of its rapid onset and short duration of action. Because of its better side effect profile, rocuronium may be the most reasonable alternative to succinylcholine. Rocuronium has a quick onset of action but longer duration of effect compared with succinylcholine. For patients requiring prolonged paralysis, nondepolarizing blocking agents are more suitable. The kinetics of nondepolarizing agents allow for a longer duration of action, more gradual onset and offset of block, and fewer hemodynamic changes. They can be administered by continuous infusion, and the blockade can be reversed, if necessary, with cholinesterase inhibitors.

The choice of agent for continuous paralysis involves clinical judgment and preference. Currently available nondepolarizing agents can be compared with one another with regard to the adverse-effect profile (histamine release and cardiovascular instability), route of elimination, drug interactions, and cost effectiveness to guide drug choice for paralysis of ventilated patients. [Table 18.4](#) compares some of these factors for several NMBAs.

TABLE 18.5 Drugs and Conditions That Interact With Nondepolarizing Neuromuscular Blocking Agents

Potentiating Factors	Antagonizing Factors
Drugs - Potent anesthetic vapors - Antibiotics - Aminoglycosides - Clindamycin - Vancomycin - Tetracycline - Local anesthetics - Antiarrhythmics - Procainamide - Quinidine - Calcium channel blockers β-Adrenergic blockers - Cyclosporine - Dantrolene - Cyclophosphamide - Lithium - Mineralocorticoids - Ethothiophate - Tacrine - Metoclopramide	- Phenytoin - Carbamazepine - Theophylline - Anticholinesterase agents - Azathioprine - Ranitidine
Conditions - Acidosis - Hyponatremia - Hypocalcemia - Hypokalemia - Hypermagnesemia - Hypothermia - Renal failure - Hepatic failure - Organophosphate poisoning	- Alkalosis - Hypercalcemia - Demyelinating injuries - Peripheral neuropathy
Diseases - Myasthenia gravis - Muscular dystrophy - Amyotrophic lateral sclerosis - Poliomyelitis - Multiple sclerosis - Eaton-Lambert syndrome	Diabetes mellitus

Data from Feldman, S. & Karalliedde, L. (1996). Drug interactions with neuromuscular blockers. *Drug Safety*, 15, 261.

Most nondepolarizing agents release histamine from mast cells. Pancuronium is thought to provoke the smallest release of histamine. Such agents as vecuronium, rocuronium, and cisatracurium are similar to pancuronium and have minimal histamine release relative to the other agents. Atracurium has been shown to induce more histamine release than pancuronium. Flushing is the most common effect of histamine release after atracurium administration. Histamine release by these drugs can be minimized by administering a bolus dose slowly over 60 seconds, administering several smaller boluses, or giving the agent by slow continuous infusion.

Vecuronium, atracurium, and cisatracurium have minimal effects on heart rate and blood pressure. Pancuronium often produces a transient increase in blood pressure and heart rate.

Rocuronium seems to cause little systemic cardiovascular effect, but an increase in pulmonary vascular resistance has been seen. Caution is recommended in using this agent in patients with pulmonary hypertension or valvular heart disease.

The method of drug elimination (e.g., renal or hepatic) is a very important factor in selecting an agent for patients with multiorgan dysfunction syndrome requiring mechanical ventilation. Agents that depend on the liver and kidney for elimination are poorly suited for patients with disease or failure of these organs. In patients with hepatic or renal failure, atracurium and cisatracurium have the advantage of plasma metabolism and do not rely on hepatic metabolism or renal excretion. The metabolite laudanosine, created from atracurium metabolism, may be of concern in patients with kidney or liver failure. Cisatracurium results in less laudanosine compared with atracurium.

Patients in the ICU have clinical conditions and are often receiving medications that can affect blockade with an NMBA. As discussed earlier, myopathy can occur in patients receiving NMBAs. The potential is increased in patients receiving concomitant corticosteroids. Steroid structured agents, such as vecuronium, pancuronium, and rocuronium, may prolong muscle weakness further. Nonsteroid-structured agents, such as atracurium or cisatracurium, may be better suited for patients requiring high-dose corticosteroids.

Finally, cost is an important consideration in choosing an agent. Many hospitals limit the number of NMBAs available on formulary because of economic issues. Newer, shorter-acting agents are very expensive, especially if used for a prolonged period in the ICU. Most hospitals restrict their use to procedures of short duration. Guidelines for blockade use in the ICU have been published and suggest that cost-effective relaxation can be provided with bolus dosing or continuous infusions of pancuronium (if tachycardia is not a concern) or vecuronium in patients with ischemic cardiovascular issues.³ For patients with hepatic and renal dysfunction, cisatracurium or atracurium is the best option. The clinician is advised to reassess the need for continuous paralysis on a daily basis.

Pancuronium provides the least expensive option for prolonged paralysis of patients who are hemodynamically stable with no organ dysfunction. In unstable patients, vecuronium produces the least amount of histamine release and fewest cardiovascular effects. Atracurium and cisatracurium offer alternative choices for ventilator management, with these agents having the advantage of alternative metabolic pathways, but at a higher cost.

CLINICAL CONNECTION

Nondepolarizing agents are preferred for induction of paralysis in ventilated patients because of the predictability, longer duration of action, and manageable side effects of these agents. Specific agents should be selected on the basis of potential for histamine release and cardiovascular effects, patient-specific metabolic pathways, and cost.

Monitoring of Neuromuscular Blockade

Patients receiving NMBAs require constant monitoring with frequent physical assessment and regularly scheduled evaluations of laboratory studies because clinical signs and symptoms of acute disease can be masked by muscle paralysis. Alarm systems to detect accidental disconnection from the ventilator are mandatory, and alarms to detect hypoventilation and hypoxemia are the standard of care when neuromuscular blockade is employed.

Before initiating neuromuscular blockade in an agitated patient, ventilator malfunction must first be ruled out as the cause of agitation, or muscle paralysis could cause death in the face of inadequate machine volume or oxygen delivery. Patients receiving paralytics can be assessed by visual, tactile, and electronic methods to evaluate the muscle tone and depth of neuromuscular blockade. Direct observation of muscle activity provides the simplest means of monitoring adequacy of blockade. The sequence of paralysis of the skeletal muscles can be monitored physically: first small, rapid-moving muscles, such as the eyelids; then the face, neck, extremities, abdomen, and intercostals; and finally the diaphragm. Recovery of paralysis is in reverse order, with recovery of the diaphragm and respiratory muscles occurring first. The sensitivity of individual muscles to paralysis is related to the number of fibers innervated by each motor neuron and by regional blood flow, with areas receiving a greater blood flow having more drug delivery and therefore a quicker onset of paralysis.

The majority of experience with NMBA occurs in the operating room. The time course of relaxant effect and rate of recovery is not the same when these drugs are used for prolonged periods in patients in the ICU. During brief periods of paralysis, the depth of blockade or the adequacy of recovery of neuromuscular function can be assessed by simple measures of voluntary muscular functions.¹¹ These include subjective assessments, such as handgrip strength or the ability to lift the head off the bed for 5 seconds. Objective assessments include measurement of vital capacity, negative inspiratory force, and spontaneous respiratory rate. Patients requiring prolonged paralysis are not as easy to evaluate because of such issues as heavy sedation. Although clinical signs may be helpful in these patients, a more physiologic and objective evaluation of neuromuscular blockade can be achieved by using electronic methods, such as peripheral nerve stimulation. Examples of modes of peripheral nerve stimulation include single twitch, double burst, train of four (TOF), and tetanic and posttetanic count.

Peripheral nerve stimulation or “twitch monitoring” is used as a monitoring tool for efficacy and toxicity in surgical and ICU patients. In peripheral nerve stimulation, a stimulator is applied to a peripheral nerve, and the response of the corresponding muscle is observed. The ulnar nerve, which innervates the adductor pollicis muscle of the thumb, is the most commonly used area.

Another nerve is the facial nerve, which innervates the orbicularis oculi muscle of the eye. The nerve response to electrical stimulation depends on the current applied, the duration for which the current is applied, and placement of the electrodes. For ulnar nerve stimulation, two small conducting pads are placed on the forearm over the nerve tract, several inches apart. A single electrical stimulus is discharged from a nerve stimulator to the ulnar nerve; the responses or twitches of the thumb that occur are then measured. As the amount of paralysis increases, the strength and degree of movement of the twitch decrease.

The most commonly used technique for monitoring blockade is the TOF evaluation, where a supramaximal stimulus at a frequency of 2 Hz is applied to the nerve over 2 seconds. The non-painful stimuli are delivered as four pulses, one every 0.5 second. The number of twitches that occur, ranging from 0 (100% blockade) to 4 (<75% blockade), are measured. Comparison of the strength of the fourth twitch and first twitch predicts the degree of receptor occupancy (Table 18.6). Clinically, the degree of blockade can be determined by counting the number of twitches seen. Four equal twitches indicate that less than 75% of the receptors are occupied with a blocker. If only three twitches are seen, approximately 80% of receptors are blocked; if only one or two are seen, 90% to 95% are blocked.

Proper placement of the conducting pads is essential to proper assessment of the TOF. The TOF evaluates the conduction of an impulse across the neuromuscular junction. If the pads are placed directly on the muscle, the patient falsely exhibits inadequate paralysis, which leads to the administration of doses of the paralytic that are higher than necessary. Although TOF evaluation is the most common method used, changes in patient condition (e.g., third spacing, anasarca) limit the utility of this test, and alternative means must be sought.

TOF monitoring allows for an accurate assessment of neuromuscular blockade depth with or without baseline control. To avoid overdosing of patients, the NMBA (bolus or infusion) should be titrated to produce the minimal blockade required to maintain the desired clinical response. Predefined goals, such as decreased oxygen requirements, peak inspiratory pressure, and positive end-expiratory pressure (PEEP) reduction, should be assessed frequently. If the response is adequate, a TOF count of

TABLE 18.6 Receptor Occupancy Associated With Various Measurements of Neuromuscular Blockade

Receptors Occupied (%)	Twitch Height (%)	Train of Four	Clinical Observations
100	0	0	Total paralysis, no voluntary movement of any muscle; no PTF
98–99	0	0	Diaphragm may move; PTF present
95–98	1–5	1 or 2 twitches	Diaphragm can move minimally; PTF and fade present
90–95	10–25	2 or 3 twitches	Breathing inadequate
75–90	10–25	4 twitches, 1st > 4th	Tidal volume restored, voluntary movement apparent, can sustain head lift for 5 seconds (75%–80% occupancy), NIP >55 cm H ₂ O, vital capacity 60%–70% of normal
50–75	100	4 equal twitches	Normal strength and movement, cough strength decreased; double burst suppression abnormal
<30	100	4 equal twitches	No apparent deficits, double burst suppression normal

cm H₂O, Centimeters of water; NIP, negative inspiratory pressure; PTF, posttetanic facilitation.

at least one twitch to two or four stimulations is recommended. It is possible that lesser degrees of blockade may achieve the clinical goal of ventilator synchrony or improved oxygenation. In the ICU, the depth of blockade should be assessed every 2 to 3 hours on initiation until a stable dose is maintained. Thereafter, TOF assessment may be performed every 8 to 12 hours. If there is no twitch response or the clinical response is achieved at a higher twitch, the dose of the NMBA should be decreased by 10%. If three or four twitches occur without adequate response, the dose can be increased by 10%. The need for continued paralysis of a patient in the ICU should be assessed daily, and if appropriate, paralysis should be discontinued as soon as possible.⁸

KEY POINT

Titration of drug dose and monitoring of reversal are performed with a peripheral nerve stimulator and train-of-four (TOF) stimulation.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. List four general uses of skeletal muscle relaxants.
2. What are the three classifications of neuromuscular blocking agents?
3. Identify each of the following agents by classification type: vecuronium, succinylcholine, and pancuronium.
4. Which type of neuromuscular blocker can be reversed?
5. What type of drug would you use to reverse vecuronium?
6. Identify another drug that you would want to give before you reverse vecuronium.
7. Briefly explain why you might need to paralyze a patient receiving mechanical ventilation.
8. Neuromuscular blocking agents do not block consciousness; what two types or classes of drugs would be indicated in a paralyzed patient on mechanical ventilation?
9. Identify at least two neuromuscular blocking agents that would be preferred for paralysis in a patient receiving mechanical ventilation (assume normal renal and hepatic function).
10. You are called to the recovery room to set up a ventilator for an elderly patient who has just undergone a total hip replacement and has stopped breathing after a single dose of succinylcholine. What might the problem be?
11. What would you do first to assess a ventilated patient who is restless and “fighting” the ventilator before using a paralyzing agent?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 64-year-old White woman comes to the emergency department with a complaint of shortness of breath and congestion along with fatigue and lethargy over the last 3 days. Her problem list includes a history of diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (COPD) secondary to smoking. She has had a cough productive of greenish yellow sputum and states she has had fever and chills over the past several days. Her current medications include metformin, glyburide, lisinopril, ipratropium inhaler, albuterol inhaler as needed, and Advair inhaler.

On physical examination, her vital signs are as follows: pulse (P) 130 beats/min, blood pressure (BP) 100/72 mm Hg, temperature (T) 38.5°C, and respiratory rate (RR) 30 breaths/min with a moderate amount of respiratory distress. On auscultation, breath sounds are diminished bilaterally.

An electrocardiogram shows sinus tachycardia. Pulse oximetry shows 80% saturation on room air. A chest radiograph shows bilateral interstitial infiltrates. Her white blood cell (WBC) count is $23.7 \times 10^9/\text{mm}^3$ with 35% bands; hemoglobin is 11.2 g/dL; hematocrit is 33.2%; and electrolytes are normal except for glucose, which is 250 mg/dL.

After approximately 3 hours of intense treatment with intravenous fluids, antibiotics, and albuterol and ipratropium nebulizations, the patient continues to be short of breath. She is anxious and exhibits labored breathing. Her heart rate (HR) ranges from 126 to 154 beats/min, RR is 32 to 40 breaths/min, BP is 85/60 mm Hg, and her mental status has deteriorated. Arterial blood gas values on a 100% nonrebreather mask are as follows: pH of 7.2, partial pressure of arterial carbon dioxide (PaCO_2) of 50 mm Hg, arterial oxygen pressure (PaO_2) of 55 mm Hg, and arterial oxygen saturation (SaO_2) of 82%.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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19

Diuretic Agents

RUBEN D. RESTREPO

CHAPTER OUTLINE

Renal Structure and Function

- Glomerular Filtration
- Electrolyte Filtration and Reabsorption
- Acid–Base Balance

Diuretic Groups

- Thiazide and Thiazide-Like Diuretics
- Loop Diuretics
- Carbonic Anhydrase Inhibitors
- Potassium-Sparing Diuretics
- Osmotic Diuretics

Diuretic Combinations

Drug Interactions

Adverse Effects

- Hypovolemia
- Hypokalemia
- Acid–Base Disorders
- Glucose Changes
- Ototoxicity

Special Situations

- Pregnancy, Lactation, and Children
- Acute Respiratory Distress Syndrome
- Diuretic Use in Neonates and Infants
- Furosemide and Fluid Overload

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define the terms pertaining to diuretic agents
2. Describe renal function, filtration, reabsorption, and acid–base balance
3. List and describe the various groups of diuretics
4. List some indications for diuretic therapy
5. List the most common adverse effects associated with the use of diuretics
6. Describe special situations related to diuretic therapy

KEY TERMS AND DEFINITIONS

Congestive heart failure (CHF) Failure of the heart to pump the blood adequately, resulting in lung congestion and tissular edema.

Diuretics Substances or drugs that promote production of urine.

Edema Swelling caused by abnormal accumulation of fluid in intercellular spaces of the body.

Glomerular filtration Mechanism whereby the fluid in blood is filtered across the capillaries of the glomerulus to be eliminated through the renal ducts.

Hypovolemia Physiologic state characterized by a decrease in total blood volume.

Nephrocalcinosis Disorder in which there is excessive accumulation of calcium in the kidney parenchyma and tubules.

Nephron Microscopic structural and functional unit of the kidney, responsible for regulating concentration of water and electrolytes and maintaining fluid balance; each kidney has approximately 2 million nephrons.

Ototoxicity Damage to the hearing or balance functions of the ear caused by drugs or chemicals.

Reabsorption Return of most of the water, sodium, amino acids, and sugar that were removed during filtration back to blood; occurs mainly in the proximal tubule of the nephron.

Synergistic effect Effect of two chemicals on an organism is greater than effect of either chemical individually.

Urine output Amount of urine produced in 24 hours; normal urine output averages 30 to 60 mL/hr.

The main purpose of **diuretics** is to increase **urine output** by excreting solutes and water (H_2O), thus eliminating excess fluid from the body. Generally, the primary goal of diuretic therapy is to reduce extracellular fluid volume (ECFV) to decrease blood pressure or to rid the body of excess interstitial fluid. **Chapter 19** summarizes the essentials of the clinical pharmacology of diuretics, briefly reviewing renal function with an emphasis on acid–base balance. The major groups of diuretics, their mechanisms of action, and common interactions and side effects are summarized. These groups include osmotic diuretics, carbonic anhydrase inhibitors (CAIs), thiazides, loop diuretics, and potassium-sparing agents.

Renal Structure and Function

The kidneys are paired retroperitoneal organs found on either side of the spinal cord at the level of the umbilicus. In an adult, each kidney weighs approximately 160 to 175 g and is 10 to 12 cm long. Kidneys receive perfusion directly from the renal artery, which provides the highest blood flow per gram of organ weight in the body. Approximately 25% of the cardiac output, or about 1.1 L/min in a normal 70-kg adult, flows through the kidneys. Similar to the heart and the brain, the kidney is an active organ (not a passive filter) with high oxygen consumption. For this reason, impaired circulation can cause renal failure or damage.

Fig. 19.1 illustrates the kidney and a **nephron**, which is the functional unit of the kidney. The nephron is composed of the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct. Nearly 75% of the almost 1 million nephrons may need to be compromised before renal disease is apparent. The renal artery branches into the afferent arteriole, which enters and forms the capillary tuft of the glomerulus. This blood flow leaves in the efferent arteriole, which forms the capillary network around the tubules and loop of Henle. This capillary network rejoins to form the renal vein.

The glomerulus is supported and surrounded by an epithelial-lined capsule named *Bowman capsule*. The glomerular capsule is actually the beginning of the proximal tubule, and filtration of

fluid from blood to the tubule occurs in the glomerulus. This fluid is the glomerular filtrate, which empties into the proximal tubule and goes through the descending and ascending loops of Henle, into the distal tubule, and later into the collecting duct. Each of the nearly 250 collecting ducts collects urine from about 4000 nephrons. The collecting ducts merge to form larger ducts that eventually empty into the renal papillae and finally empty into the ureter to be stored in the bladder.

The principal function of the nephron is to maintain homeostasis or equilibrium between the internal volume and electrolyte status and the influences of the environment, diet, and intake. This mission is accomplished by almost 2 million nephrons through the processes of glomerular ultrafiltration, tubular reabsorption, and tubular secretion. The kidney cannot regenerate new nephrons.

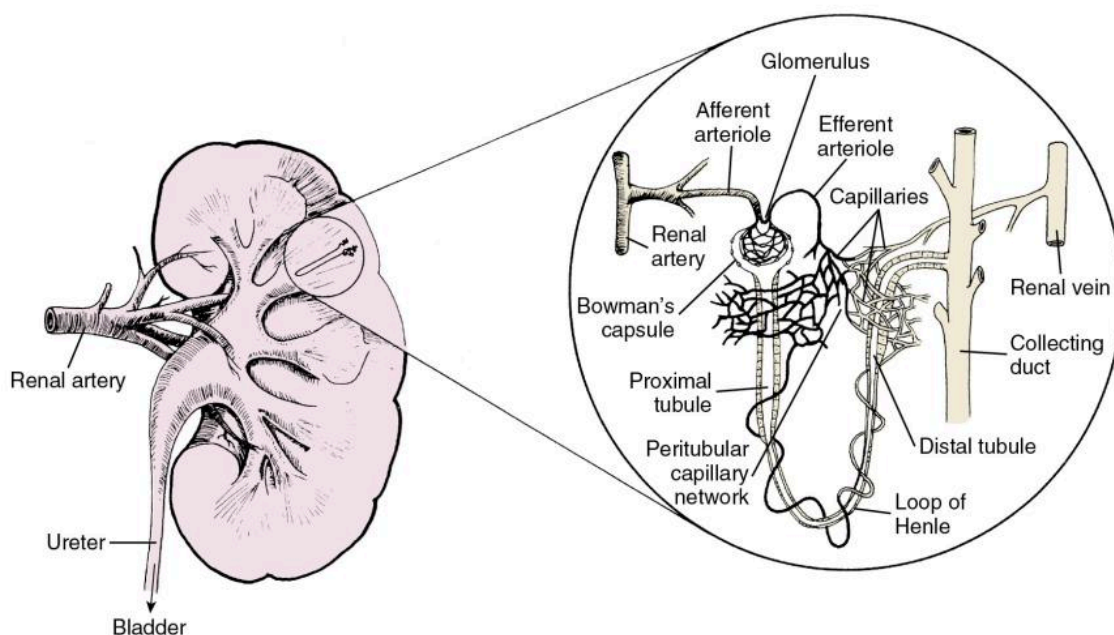
Renal injury, disease, and aging are associated with a gradual decrease in the number of nephrons. The body maintains blood pressure at the expense of ECFV. Control of ECFV is achieved by adjusting sodium chloride (NaCl) and H_2O excretion.

Glomerular Filtration

Glomerular filtration begins in the glomerulus, the nephron forms a cell-free ultrafiltrate with a relatively small amount of protein, which has the same ionic concentration (e.g., sodium [Na^+], chloride [Cl^-], bicarbonate [HCO_3^-]) as plasma. Of the total blood flow that goes through the nephron, 20%, or about 130 mL/min, is filtered through the glomerulus. Greater than 99% of this glomerular filtrate is reabsorbed in the tubules, and less than 1% of the fluid is excreted as urine. The total urine output for an adult is approximately 0.5 to 1 mL/min, or about 30 to 60 mL/hr. Because diuretics interfere with the **reabsorption** of H_2O in the tubules of the nephron, they increase the urine output.

Electrolyte Filtration and Reabsorption

The ions listed in **Box 19.1** are filtered and exchanged in the tubules.



• **Fig. 19.1** Basic structure of the kidney, with a detailed view of the nephron.

• BOX 19.1 Common Electrolytes

- Sodium (Na^+)
- Potassium (K^+)
- Chloride (Cl^-)
- Bicarbonate (HCO_3^-)
- Hydrogen (H^+)
- Calcium (Ca^{++})
- Magnesium (Mg^{++})

- **Sodium:** About 70% of Na^+ in the filtrate is reabsorbed in the proximal tubules; 20%, in the loops of Henle; and about 10%, in the distal tubules. There is an exchange of Na^+ for hydrogen (H^+) or potassium (K^+) in the distal tubules.
- **Potassium:** Most filtered K^+ is reabsorbed in the proximal tubules. K^+ found in urine is that secreted by the distal tubule.
- **Chloride and bicarbonate:** Cl^- and HCO_3^- are passively reabsorbed in the proximal and distal tubules.

KEY POINT

Urine output greater than 100 mL/day but less than 400 mL/day in adults and less than 0.5 mL/kg/hr in children is known as *oliguria*. Urine output greater than 60 mL/hr is known as *polyuria*. Oliguria and *anuria* (less than 50 mL/day) are often signs of renal failure.

H_2O is also passively reabsorbed or excreted, depending on the concentration of electrolyte, primarily Na^+ , in the filtrate. By inhibiting Na^+ reabsorption, diuretics cause less H_2O to be retained and more excreted in the filtrate.

Aldosterone, a mineralocorticoid secreted by the adrenal cortex, increases Na^+ and H_2O reabsorption in the distal tubule. Spironolactone is a diuretic that increases Na^+ and H_2O loss by inhibiting aldosterone.

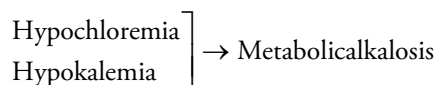
Acid–Base Balance

Because a fundamental function of the kidney is the control of buffering substances, especially HCO_3^- , diuretics may cause acid–base imbalances to occur because they increase H_2O loss. Fig. 19.2 illustrates the H^+ and HCO_3^- pathways that regulate pH. The filtration and reabsorption of Na^+ , Cl^- , and HCO_3^- , described previously, can be seen in Fig. 19.2.

The important exchange for acid–base balance is that of Na^+ . Na^+ is reabsorbed in the tubules by several means, as follows:

- Reabsorption with Cl^- to preserve electrical neutrality
- Exchange of Na^+ for H^+ or K^+ , also to preserve neutrality

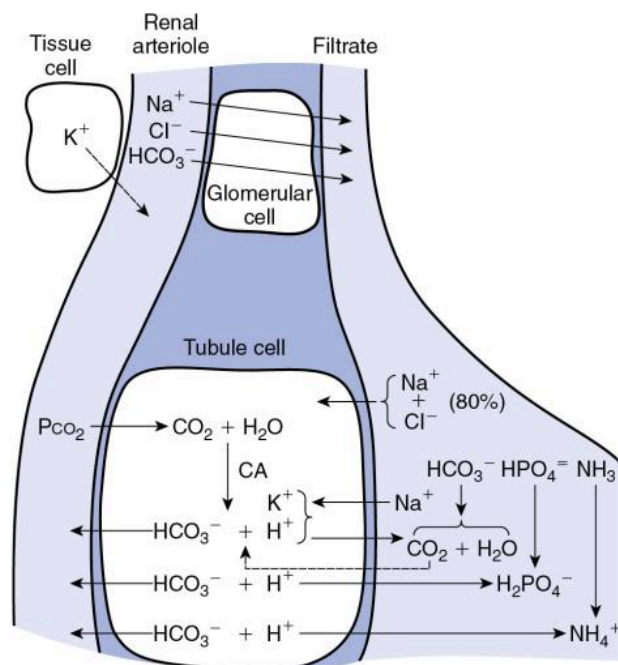
Either low Cl^- (hypochloremia) or low K^+ (hypokalemia) forces Na^+ to exchange for H^+ , producing a loss of H^+ and metabolic alkalosis.



Finally, preventing HCO_3^- in the *filtrate* from forming carbon dioxide (CO_2) and water (H_2O) results in a loss of HCO_3^- buffer in the urine and metabolic acidosis.

Diuretic Groups

The primary therapeutic goal of diuretic use is to reduce the ECFV. NaCl output *must* exceed NaCl intake. Diuretics primarily



• **Fig. 19.2** Basic mechanisms for kidney retention of bicarbonate with hydrogen ion buffering. Sodium exchange with chloride and for hydrogen is also indicated. CA, Carbonic anhydrase; Cl^- , chloride ion; CO_2 , carbon dioxide; H^+ , hydrogen ion; H_2O , water; H_2PO_4^- , dihydrogen phosphate ion; HCO_3^- , bicarbonate ion; HPO_4^{2-} , hydrogen phosphate ion; K^+ , potassium ion; Na^+ , sodium ion; NH_3 , ammonia; NH_4^+ , ammonium; PCO_2 , partial pressure of carbon dioxide.

prevent Na^+ entry into the tubule cell. Diuretics need to access the tubule fluid to exert their action. Once in the tubule fluid, the nephron site at which the diuretic acts determines its effect. The site of action also determines which electrolytes, other than Na^+ , are affected. All diuretics except spironolactone exert their effects from the luminal side of the nephron.¹

Five major groups of diuretics are described in this chapter. Fig. 19.3 illustrates the site of action, and Table 19.1 summarizes the mechanism of action and the indications for use of each of the five major groups of diuretics.^{2,3}

Hypertension affects over 1.1 billion people worldwide and nearly half of the adults in the United States⁴; the diuretics of most immediate relevance to respiratory and critical care clinicians are those used to treat hypertension and **congestive heart failure (CHF)**. Diuretics are the second most commonly prescribed class of antihypertensive medication, and diuretic-based therapy is effective in reducing morbidity and mortality among patients with moderate to severe hypertension.¹ Furthermore, irrespective of salt sensitive status, large meta-analyses have shown that low-dose diuretics compared to other antihypertensives have demonstrated superiority and have the most evidence available.^{1,5}

KEY POINT

Diuretic agents are important in reducing the morbidity and mortality of patients with cardiovascular disease who have fluid retention.

Thiazide and Thiazide-Like Diuretics

High-quality evidence and most guidelines recommend that low-dose thiazides should be used first for most patients with

• **Fig. 19.3** Illustration of the nephron, from glomerulus to collecting duct, showing various sites of action for diuretic groups. CA, Carbonic anhydrase; H^+ , hydrogen ion; H_2O , water; HCO_3^- , bicarbonate ion; K^+ , potassium ion; Na^+ , sodium ion; $NaCl$, sodium chloride. 1–5, Points at which the five major groups of diuretics exert their effects.

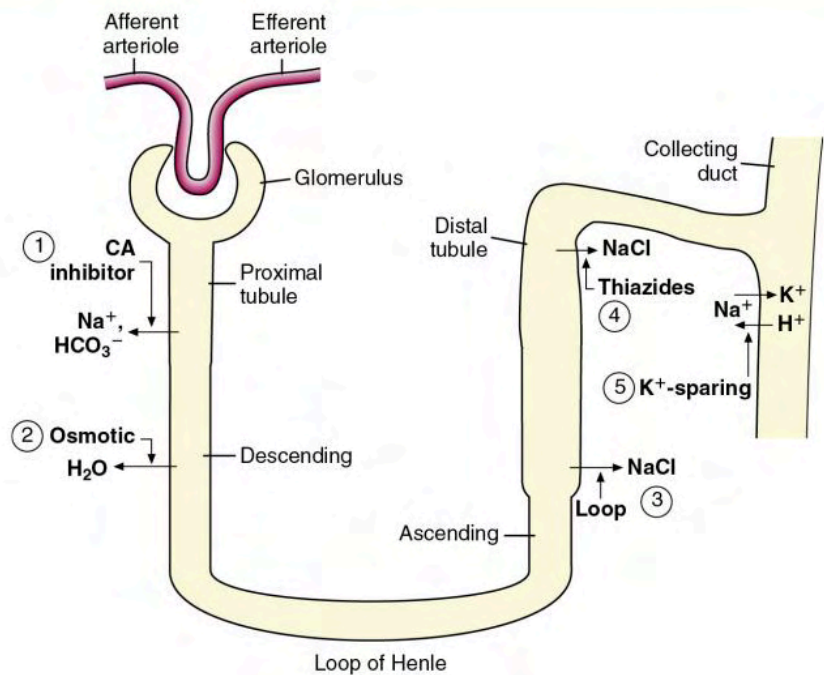


TABLE 19.1

Site and Mechanism of Action, Main Indications, and Other Uses of Diuretics

Diuretic Class (Mechanism of Action)	Main Indications	Other Uses
Osmotic Diuretics		
Freely filtered, nonreabsorbable osmotic agents such as mannitol, glycerol, and urea: Reduction of reabsorption of H_2O and solutes, including $NaCl$, primarily in proximal tubule and descending loop of Henle	To treat or prevent ARF	To reduce intracranial or intraocular pressure; bronchial challenge
Carbonic Anhydrase Inhibitors		
Acetazolamide, methazolamide, and dichlorphenamide: Inhibition of carbonic anhydrase in luminal membrane of proximal tubule, reducing proximal sodium and bicarbonate reabsorption	To reduce intraocular pressure in glaucoma; to lower HCO_3^- in mountain sickness; to increase urine pH in cystinuria	Periodic paralysis; adjunctive therapy in epilepsy; hydrocephalus
Loop Diuretics		
Furosemide, bumetanide, torsemide, and ethacrynic acid: Inhibition of $Na^+/K^+/Cl^-$ reabsorption in thick ascending limb of Henle	Hypertension, CHF (in the presence of renal insufficiency or for immediate effect); ARF; CRF, ascites, and nephrotic syndrome	Acute pulmonary edema; to enhance urinary excretion of chemical toxins; hypercalcemia; nonobstructive oliguria; renal transplant; autism
Thiazide Diuretics		
Chlorothiazide, hydrochlorothiazide, chlorthalidone, hydroflumethiazide, methyclothiazide, bendroflumethiazide, polythiazide; thiazide-like diuretics: metolazone, indapamide, chlortalidone; Inhibition of $NaCl$ reabsorption in early DT	Hypertension; CHF; idiopathic hypercalciuria (renal calculi)	Nephrogenic diabetes insipidus (prevent further urine dilution from taking place in DT); CRF
Potassium-Sparing Diuretics		
Spironolactone and eplerenone: Competitively block actions of aldosterone on CCDs	Chronic liver disease: To treat secondary hyperaldosteronism caused by hepatic cirrhosis complicated by ascites	Primary hyperaldosteronism (Conn syndrome); acne; alopecia; hirsutism
Amiloride and triamterene: Inhibition of the Na^+/K^+ pump by reducing Na entry across luminal membrane of CCDs	CHF: To counteract hypokalemic effect of other diuretics	

ARF, Acute renal failure; CCDs, cortical collecting ducts; CHF, congestive heart failure; CRF, chronic renal failure; DT, distal tubule; HCO_3^- , bicarbonate concentration.

TABLE 19.2 Characteristics of Diuretics

Drug	Route	Onset (min)*	Peak (hr)	Duration (hr)	Half-Life (hr)	Oral Bioavailability (%)	Typical Dosage
Osmotic							
Glycerin	PO	10–30	1–1.5	4–5	0.5–0.75	ND	1–2 g/kg
Isosorbide	PO	10–30	1–1.5	5–6	5–9.5	ND	1–3 g/kg
Mannitol	IV	30–60	1	6–8	0.25–1.5	NA	50–100 g
Urea	IV	30–45	1	5–6	NA	NA	1–1.5 g/kg
Loop							
Bumetanide	PO	30–60	1–2	4–6	1–1.5	72–96	0.5–2.0 mg
	IV	5	0.25–0.5	0.5–1	1–1.5	72–96	0.5–2.0 mg
Ethacrynic acid	PO	30	2	6–8	1	100	50–100 mg
	IV	5	0.25–0.5	2	1	100	50–100 mg
Furosemide	PO	60	1–2	6–8	2	60–64	20–80 mg
	IV	5	0.5	2	2	60–64	20–80 mg
Torsemide	PO	60	1–2	6–8	3.5	80	5–20 mg
	IV	10	<1	6–8	3.5	80	5–20 mg
Thiazide							
Bendroflumethiazide	PO	120	4	12–16	3–4	100	5 mg
Benzthiazide	PO	120	4–6	16–18	ND	ND	50–100 mg/day
Chlorothiazide	PO	120	4	12–16	0.75–2	10–21	0.5–2.0 g/day
	IV	15	0.5	12–16	0.75–2	10–21	0.5–2.0 g/day
Chlorthalidone	PO	120–180	2–6	24–72	40	64	50–100 mg/day
Hydrochlorothiazide	PO	120	4–6	12–16	50.6–14.8	65–75	50–200 mg/day
Hydroflumethiazide	PO	120	4	12–16	17	50	25–200 mg/day
Indapamide	PO	60–120	<2	36	14	93	1.25–5 mg/day
Methyclothiazide	PO	120	6	24	ND	ND	5 mg
Metolazone	PO	60	2	12–24	ND	65	5–20 mg/day
Polythiazide	PO	120	6	24–48	25–37	ND	2–4 mg/day
Quinethazone	PO	120	6	18–24	ND	ND	50–100 mg/day
Trichlormethiazide	PO	120	6	24	2.3–7.3	ND	2–4 mg/day
Potassium Sparing							
Amiloride	PO	2 hr	6–10	24	6–9	30–90	5–20 mg/day
Spironolactone	PO	24–48 hr	48–72	48–72	20	73	25–400 mg/day
Triamterene	PO	2–4 hr	6–8	12–16	3	30–70	200–300 mg/day

*Unless otherwise indicated.

IV, Intravenous; NA, not applicable; ND, no data; PO, oral.

elevated blood pressure as they reduce all morbidity and mortality outcomes in adult patients with moderate to severe primary hypertension. These outcomes include mortality, stroke, coronary heart disease, and total cardiovascular events. On the other hand, while high-dose thiazides significantly reduce stroke and total

cardiovascular events, they increase the risk for toxicity and do not reduce mortality or coronary heart disease.⁵

Thiazide and thiazide-like diuretics (see Table 19.2) block NaCl reabsorption at the distal convoluted tubule.³ The results of a systematic review showed that thiazide-like diuretics like

chlorthalidone (CTDN) alleviated hypertensive burden by about 5.1 mmHg of systolic blood pressure more than the well-known thiazide-type diuretic hydrochlorothiazide (HCTZ), finding chlorthalidone more potent than HCTZ.⁶

In addition to potency, studies have demonstrated that CTDN holds a longer duration of action than HCTZ, 24 hours with CTDN versus 6 to 12 hours with HCTZ. This increased duration of action allows for the increased flexibility of dosing. A study has shown that as a result of this longer duration of action that chlorthalidone is 1.5 to 2.0 times more efficacious at lowering systolic blood pressure than HCTZ (comparative antihypertensive effects between hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure).⁷

In addition to its diuretic effects, indapamide lowers systolic blood pressure via a calcium-like vasorelaxant effect and its potency is greater than HCTZ.⁸

CLINICAL CONNECTION

Thiazide diuretics are considered the first-line therapy for mild hypertension.

Loop Diuretics

The loop diuretics (see Table 19.2) are potent and widely used agents in the therapy of edematous states and congestive heart failure and less commonly for hypertension. They are often called “high ceiling” diuretics because they can cause up to 20% of the filtered load of NaCl and H₂O to be excreted in the urine. The loop diuretics are more potent than the typical thiazide diuretics and usually have a shorter duration of action. They act by inhibition of the sodium-potassium-chloride symporter present in the thick ascending limb of the loop of Henle causing an inhibition of sodium reuptake, thus increasing Na⁺, K⁺, Cl⁻, and H₂O excretion.²

When administered intravenously, loop diuretics produce an acute hemodynamic effect independent of their diuretic properties.^{2,9} Within 5 minutes of administration of intravenous loop diuretics to patients with cardiac disease, an acute vasodilatory effect is observed.¹⁰ This effect manifests as a decrease in pulmonary capillary wedge pressure (PCWP), blood pressure, and systemic vascular resistance. The effect seems to be derived from the renal release of vasodilating prostaglandins.^{11,12}

Because the diuretic effect of intravenous loop diuretics is typically not seen for 15 to 20 minutes after administration, patients with acute pulmonary edema may derive a clinical benefit from intravenous loop diuretics before the onset of diuresis. The hemodynamic effect is short-lived, with all measurements returning to baseline once diuresis has begun.

The acute hemodynamic effect has also been reported to activate the sympathetic nervous system, resulting in an adverse hemodynamic profile characterized by increased afterload and diminished cardiac function before the onset of diuresis.¹¹ This effect is also short lived and dissipates with the onset of diuresis. Because the diuretic effect may last several hours, several doses per day may be required to maintain a net diuretic effect for 24 hours. Patients requiring frequent bolus doses may benefit from continuous infusion.

KEY POINT

Loop diuretics produce a hemodynamic effect characterized by acute vasodilation and manifest as a decrease in pulmonary capillary wedge pressure (PCWP), blood pressure, and systemic vascular resistance.

Administration of loop diuretics to patients with renal dysfunction results in less total drug reaching the site of action within the nephron, and the administration of larger doses is required to achieve a therapeutic effect.^{13,14}

In these patients, the effects of furosemide, bumetanide, and torasemide differ. Furosemide may have a more prolonged effect in patients with renal dysfunction. However, patients may be resistant to furosemide compared with bumetanide. Because loop diuretics are the most potent diuretics, they are effective at very low creatinine clearance levels (a low creatinine clearance level indicates kidney disease). Loop diuretics as single agents should be considered as first-line therapy in patients with creatinine clearance values less than 40 mL/min. If this dose is inadequate to produce diuresis within 20 minutes, the dose can be doubled every 20 minutes until a response occurs or until a maximum dose is reached. Various studies have reported a ceiling effect to furosemide of approximately 250 mg. Increasing the dose above this ceiling dose may not produce an increased response.¹⁵

Although patients with renal dysfunction require larger doses to deliver diuretics into urine, the remaining nephrons in these patients continue to function normally. Overall, Na⁺ excretion may be limited as a result of diminished Na⁺ filtration. To overcome this relative resistance, an effective response may be obtained by administering a large enough dose several times a day. Certain disease states result in a diminished response that does not improve with administration of larger doses. Although the mechanism for this effect is unknown, it has been reported in patients with CHF, cirrhosis, and nephrotic syndrome.¹⁵ In these patients, multiple doses should be given, rather than larger single doses. This finding implies a modest ceiling dose of loop diuretics in patients with CHF and cirrhosis.

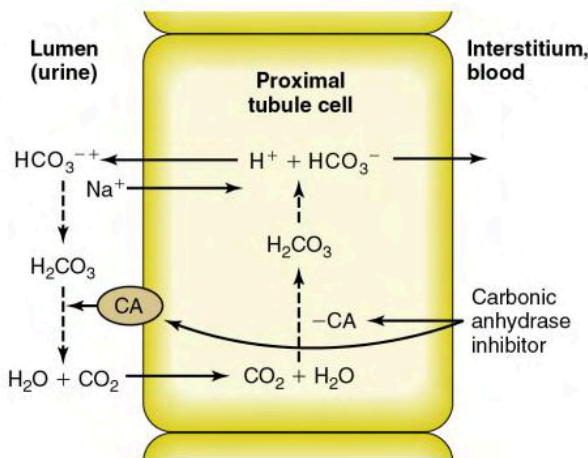
Common and shared side effects of the loop diuretics include dizziness, headache, gastrointestinal upset, hypernatremia, hypokalemia and dehydration. Uncommon but potentially severe adverse events include profound electrolyte and water loss, dehydration leading to hypotension and syncope, electrolyte depletion with hypokalemia, hypomagnesemia, and hyponatremia, increases in serum creatinine and uric acid with worsening of renal failure and precipitation of hepatic encephalopathy in patients with cirrhosis, hyperuricemia, gout, ototoxicity, thrombocytopenia and hypersensitivity reactions.

Although loop diuretics remain the mainstay of treatment for relieving congestion in patients with heart failure (HF), the most comprehensive, to date, review of associations of LD use and dose with hard clinical outcomes in patients with HF demonstrated that loop diuretics, especially in high doses, are associated with increased all-cause mortality in patients with HF. The use of loop diuretics is also associated with higher rates of HF hospitalizations.¹⁶

Carbonic Anhydrase Inhibitors

The primary site of action of CAIs is within the proximal tubule. Carbonic anhydrases are enzymes that catalyze the hydration of CO₂ and the dehydration of HCO₃⁻: CAIs prevent the normal breakdown of carbonic acid and thus decrease HCO₃⁻ reabsorption.

CAIs inhibit transport of HCO₃⁻ into the interstitium from the proximal convoluted tubule. Therefore, less Na⁺ is reabsorbed, causing greater Na⁺, HCO₃⁻, and H₂O loss in urine, resulting in a net increased flow of alkaline urine (Fig. 19.4). The potential for metabolic acidosis coupled with their weak diuretic properties limits the use of CAIs as the first-line treatment for patients who require more aggressive management of their hypervolemic status.



• **Fig. 19.4** Effect of carbonic anhydrase inhibitor diuretics, such as acetazolamide, which block the availability of hydrogen to exchange for sodium in the proximal tubule, causing a loss of sodium, bicarbonate, and water, along with reduced bicarbonate reabsorption into cells and blood. CA, Carbonic anhydrase; CO_2 , carbon dioxide; H^+ , hydrogen ion; H_2CO_3 , carbonic acid; H_2O , water; HCO_3^- , bicarbonate ion; Na^+ , sodium ion.

Other, more common uses of CAIs include treatment of glaucoma, metabolic alkalosis, and altitude sickness. Carbonic anhydrase is an important enzyme in the formation of intraocular fluid. CAIs effectively decrease intraocular pressure and are used to treat glaucoma. Short-term CAIs may also correct metabolic alkalosis as a result of the acidosis they produce. Finally, CAIs have been shown to be useful against altitude sickness, although the exact mechanism of action is unknown. The most common adverse effect of CAIs is hypokalemia resulting from the increased amount of Na^+ that is presented to the collecting duct and is reabsorbed in exchange for K^+ excretion.

CLINICAL CONNECTION

Osmotic diuretics are often used in the management of patients with traumatic brain injury who have cerebral edema.

KEY POINT

Although carbonic anhydrase inhibitors (CAIs) are considered to be very weak diuretics, they are commonly used in patients with glaucoma, metabolic alkalosis, and altitude sickness.

Potassium-Sparing Diuretics

Potassium-sparing diuretics increase urine output by interfering with the Na^+ and K^+ exchange in the distal convoluted tubule (*Amiloride* and *triamterene*) or by acting as an antagonist at the aldosterone receptor (*spironolactone*) (see Table 19.2). The antagonism of the aldosterone-induced vasoconstriction is associated with a 6 to 8 mm Hg reduction in diastolic and mean pressure in patients with end-stage renal disease. Its onset of action is between 2 to 4 hours and its maximum effect with a single dose is 7 hours but 2 to 3 days with multiple doses. On the basis of its mechanism of action, spironolactone is specifically used for conditions known to have elevated aldosterone concentrations, such as hyperaldosteronism (primary and secondary), cirrhosis and ascites, adrenal hyperplasia, and renal artery stenosis. The most common use is in

patients with cirrhosis and ascites. Because the duration of effect of spironolactone could be for several days, the dose should be increased every 3 or 4 days until the desired level of diuresis is attained.

In the distal tubule, Na^+ is typically exchanged for K^+ and H^+ . Blocking this exchange is what makes these agents *potassium-sparing diuretics*. Although frequently used in combination with thiazide diuretics to produce better diuresis and to diminish K^+ loss, the rationale for this is controversial. Only about 5% of patients receiving thiazide diuretics become K^+ depleted.¹⁷

In addition, potassium-sparing agents may produce hyperkalemia, which is a more life-threatening situation than K^+ depletion.

Triamterene is a short-acting agent used in the therapy of edema. Triamterene must be converted to an active metabolite by the liver, and this agent may be a poor choice in patients with liver dysfunction.¹⁷

Amiloride has a moderately long half-life and does not require metabolic activation. Coadministration of K^+ supplements, angiotensin-converting enzyme inhibitors, and nonsteroidal antiinflammatory agents, as well as renal dysfunction, may predispose patients receiving potassium-sparing diuretics to develop hyperkalemia.¹⁷

Osmotic Diuretics

Osmotic diuretics (Table 19.2) are freely filtered at the glomerulus but are not reabsorbed. These agents remain in the tubule lumen and impair the ability of the proximal tubule and the thick ascending limb of Henle to reabsorb NaCl . The net result is that osmotic substances are potent diuretics that lead to increased excretion of H_2O and NaCl . The resultant increased delivery of Na^+ and Cl^- to the distal tubule results in increased exchange of Na^+ for K^+ , producing a net K^+ loss in urine.

Of the four currently available osmotic diuretics (glycerin, isosorbide, mannitol, and urea), mannitol is the preferred agent because of its lower toxicity. Mannitol has a relatively short half-life and has rapid onset and offset of action. To maintain a continued diuretic action, the drug is frequently administered via continuous infusion. Patients with increased intracranial pressure due to traumatic brain injury generally require pharmacologic therapies and often surgical interventions to maintain or re-establish adequate cerebral blood flow and prevent herniation. Regardless of the cause of increased intracranial pressure, osmotherapy is considered the mainstay of medical therapy, and should be administered as soon as possible.^{18,19}

Inhaled mannitol is a bronchoconstrictor. It is available in dry powder inhaler (DPI) form (Aridol/Osmohale) as Aridol and is used to assess bronchial hyperresponsiveness in patients who are 6 years of age or older and do not have clinically diagnosed asthma. During a mannitol challenge test, the subject inhales increasing doses of mannitol with their forced expiratory volume in one second (FEV_1) measured after each dose to determine the level of bronchial hyperresponsiveness. Aridol should not be performed in any patient with clinically apparent asthma or very low baseline pulmonary function tests (e.g., $\text{FEV}_1 < 1.5$ liters or $< 70\%$ of the predicted values).

Diuretic Combinations

Various diuretic combinations may be used in an attempt to obtain an additive or synergistic effect in patients who respond poorly to one agent. By using agents with different sites of action

within the nephron, the diuretic response may be enhanced. The most common combination is of a loop diuretic and a thiazide. Although not consistently effective, combinations occasionally may result in pronounced diuresis.

Drug Interactions

Because diuretics are commonly prescribed in combination with other medications, knowledge of drug interaction plays an important role in the selection of the diuretic agent. Clinicians who prescribe diuretics need to be informed of associated comorbidities, such as diabetes, renal disease, hepatic disease, or gout. Table 19.3 summarizes some of the most common drug interaction side effects associated with diuretic agents.

Adverse Effects

Although diuretics have been used successfully for more than 40 years, they have the potential to cause adverse effects (Table 19.4). Most complications associated with diuretic use can be anticipated as an extension of their pharmacologic activity, with hypovolemia and electrolyte and acid–base abnormalities being the most common. Rare side effects that need immediate medical attention include the following:

- Black, tarry stools
- Blood in urine or stools
- Cough or hoarseness
- Falls²⁰
- Fever or chills
- Joint pain
- Pain in the lower back or side
- Painful or difficult urination
- Pinpoint red spots on the skin
- Ringing or buzzing in the ears
- Any loss of hearing
- Skin rash or hives
- Severe stomach pain with nausea and vomiting
- Unusual bleeding or bruising
- Yellow eyes or skin
- Yellow vision

TABLE 19.3 Drug Interactions and Their Potential Side Effects Associated With Use of Diuretics

Interacting Drug	Potential Side Effect
Angiotensin-converting enzyme inhibitors <i>AND</i> potassium-sparing diuretics	Hyperkalemia and cardiac irritability
Aminoglycosides <i>AND</i> loop diuretics	Ototoxicity and nephrotoxicity
Digoxin <i>AND</i> thiazide and loop diuretics	Hypokalemia
β blockers <i>AND</i> thiazide diuretics	Hyperglycemia, hyperlipidemia, hyperuricemia
Steroids <i>AND</i> thiazide and loop diuretics	Increased risk of hypokalemia
Carbamazepine or chlorpropamide <i>AND</i> thiazide diuretics	Increased risk of hyponatremia

Other adverse effects are even rarer or idiosyncratic and cannot be anticipated or prevented. There is a particular concern with the suggested association between long-term diuretic therapy and the risk of developing renal cell carcinoma.

KEY POINT

Hypovolemia and acid–base abnormalities are the most common side effects of diuretic therapy.

Hypovolemia

Because diuretics promote Na^+ and fluid excretion, elimination may exceed intake, resulting in **hypovolemia**. Hypovolemia should be suspected if dizziness, extreme thirst, excessive dryness of the mouth, decreased urine output, dark-colored urine, or constipation is observed. Certain situations may predispose a patient

TABLE 19.4 Common Side Effects of Diuretic Therapy

Drug	Effect
Osmotic diuretics	Acute expansion of ECFV and increased risk of pulmonary edema Acute hyperkalemia Nausea and vomiting; headache
Loop diuretics	<i>Depletions:</i> Hypokalemia; hypomagnesemia; hyponatremia; hypovolemia <i>Retention:</i> Hyperuricemia <i>Metabolic:</i> Hyperglycemia (insulin resistance) Metabolic alkalosis (partly secondary to ECFV reduction) Ototoxicity and diarrhea (mainly with ethacrynic acid)
Thiazide diuretics	<i>Depletions:</i> Hypokalemia, hyponatremia, hypovolemia <i>Retentions:</i> Hyperuricemia secondary to enhanced urate reabsorption; hypercalcemia secondary to enhanced Ca^{++} reabsorption Metabolic alkalosis (hypochloremia) <i>Metabolic:</i> Hyperglycemia (insulin resistance), hyperlipidemia Hypersensitivity (fever, rash, purpura, anaphylaxis) Interstitial nephritis
Potassium-sparing diuretics	<i>Spironolactone:</i> Hyperkalemia, gynecomastia, hirsutism, menstrual irregularities, testicular atrophy (with prolonged use) <i>Amiloride:</i> Hyperkalemia, glucose intolerance in diabetic patients <i>Triamterene:</i> Hyperkalemia; megaloblastic anemia in patients with liver cirrhosis
Carbonic anhydrase inhibitors	Metabolic acidosis (secondary to HCO_3^- depletion) Drowsiness, fatigue, CNS depression, paresthesia

Ca^{++} , Calcium; CNS, central nervous system; ECFV, extracellular fluid volume; HCO_3^- , bicarbonate.

• BOX 19.2 Causes of Volume Depletion With Diuretics

- Initiation of treatment or increased dose
- Improved compliance
- Reduced dietary sodium intake
- Development of diarrhea
- Ingestion of drugs that impair diuretic administration
- Improved underlying disease state not requiring diuretics

to hypovolemia (Box 19.2). Diuretic-induced hypovolemia should be treated by discontinuation of the diuretic. Mild cases of hypovolemia may respond to liberalization of Na^+ intake, whereas more severe cases require intravenous volume replacement.

Hypokalemia

Preserving K^+ balance has emerged as one of the most important factors in the management of hypertension. K^+ is exchanged for Na^+ in the distal convoluted tubule and collecting duct. Any diuretic that increases Na^+ delivery to these regions may potentially induce hypokalemia. In addition to a direct K^+ loss, diuretic-induced volume depletion produces reabsorption of Na^+ via release of aldosterone in the distal tubule in an effort to bolster intravascular volume. This additional Na^+ reabsorption also contributes to K^+ excretion. Dietary Na^+ intake and Cl^- depletion may also influence K^+ excretion. Diuretic-induced hypokalemia apparently is dose related, with loop diuretics having a lower incidence compared with thiazide diuretics.²¹

Although some studies have tried to identify the incidence of diuretic-induced hypokalemia, it is impossible to predict whether a particular patient will develop hypokalemia. The issue of K^+ supplementation is also controversial. Who to treat, when to treat, and how to treat hypokalemia all are unresolved questions. At the center of this unresolved issue is whether hypokalemia poses a risk for arrhythmias or sudden cardiac death. Supplemental K^+ should be considered in patients with a history of cardiac disease, patients with symptoms indicating hypokalemia, patients with a serum K^+ level less than 3 mEq/L, and patients receiving digitalis therapy. Potassium-sparing diuretics may induce a hyperkalemic state in 8.6% of patients receiving spironolactone and in 23% of patients receiving a potassium-sparing diuretic and K^+ supplementation.

Acid–Base Disorders

With diuresis and volume depletion, hypokalemia and hypochloremia may result. This state may cause metabolic alkalosis, which is responsive to K^+ and Cl^- replacement therapy. Exceptions are CAIs, the use of which may result in metabolic acidosis.

Glucose Changes

Thiazides are also known to be the antihypertensive drugs with the strongest diabetogenic activity.²² The average increase in serum glucose is 6.5 to 9.6 mg/dL, although cases of diabetic ketoacidosis have also been reported. The severity of glucose elevation in these reports was related to the dose of diuretic used and to the decrease in K^+ levels. Although the cause of hyperglycemia is not completely understood, several possible etiologies have been postulated, including decreased pancreatic insulin release and insulin resistance with impaired uptake of glucose in response to insulin.²³

Ototoxicity

Loop diuretics may cause a dose-related **ototoxicity** consisting of tinnitus and clinical or subclinical hearing loss. Ototoxicity results from anatomic and chemical abnormalities produced within the inner ear. Ototoxicity is related to the blood level of these agents. Rapid infusion and drug accumulation with large parenteral doses in renal failure both predispose patients to ototoxicity. Reducing the infusion rate or administering the drug orally may alleviate hearing loss.²⁴

Most ototoxicity is reversible; however, cases of irreversible hearing loss have occurred. Ethacrynic acid has a higher likelihood of causing irreversible hearing loss. Limited data on bumetanide indicate that it may have a lower incidence of ototoxicity compared with furosemide and ethacrynic acid.²⁵

Special Situations

Pregnancy, Lactation, and Children

Diuretics are not recommended for pregnant women because the effects of the drug on the fetus are unknown. Because many diuretics pass into breast milk, diuretics are not recommended to breastfeeding women because of the risk of dehydration in the infant.

Children can safely take diuretics because the side effects are similar to the side effects in adults. However, smaller doses of the drug should be used in children (Table 19.5).²⁶

Furosemide is one of the most effective and least toxic diuretics used in pediatric practice. However, long-term use of loop diuretics in children should be carefully evaluated because of the risk of **nephrocalcinosis** and potential decrease in bone mass density.²⁷

Acute Respiratory Distress Syndrome

A pathophysiologic landmark of acute respiratory distress syndrome (ARDS) is the presence of protein-rich, noncardiogenic pulmonary edema.²⁸ Compared to healthy subjects, ARDS patients present a higher amount of extravascular lung water and a linear increase in the fluid shift from capillaries to alveoli due to increasing pulmonary artery pressures.²⁹ Thus, a strategy aimed at limiting fluid accumulation into the lung can potentially improve outcome. A reduction in pulmonary artery pressures has been associated with increased survival in patients with ARDS.³⁰

Intravenous fluids are widely used to treat circulatory deterioration in pediatric acute respiratory distress syndrome (PARDS). However, early fluid restriction studied in the animal model did not limit the formation of pulmonary edema, suggesting that in the early phase of PARDS, a restrictive fluid strategy may not be beneficial in terms of immediate cardiopulmonary effects.³¹

The ARDS Network published the results of the Fluid And Catheter Treatment Trial (FACTT), in which patients who were not in shock and who were managed with a protocolized fluid management plus furosemide (conservative fluid management arm) had significantly more ventilator-free days, more intensive care unit (ICU)–free days, and lower mortality compared with those in the liberal fluid management arm.³²

Inhaled furosemide has been explored in the management of ARDS for showing significant anti-inflammatory properties by inhibition of the cytokine production associated and activation of the innate immune system.³³ Interestingly, furosemide's anti- activities do not require systemic administration of the drug and have been explored as an option for managing patients with COVID-19.³³

TABLE 19.5 Pediatric Dosages of Commonly Prescribed Diuretics

Drug	Age of Patient	Route	Typical Dosage
Furosemide	Neonates	PO	1–4 mg/kg/dose once or twice daily
		IV/IM	1–2 mg/kg/dose q12–24h
Bumetanide	Children	PO/IV/IM	1–2 mg/kg/dose q6–12h
		PO/IV/IM	ND
	>6 mo	PO/IV/IM	0.015 mg/kg/dose qid or qod; maximum 0.1 mg/kg/dose
Hydrochlorothiazide	<6 mo	PO	2–3.3 mg/kg/day divided bid
	>6 mo	PO	2 mg/kg/day divided bid
Chlorothiazide	<6 mo	PO	20–40 mg/kg/day divided bid
		IV	2–8 mg/kg/day divided bid
	>6 mo	PO	20 mg/kg/day, divided bid
Metolazone	Children	PO	0.2–0.4 mg/kg/day, divided q12–24h
		IV	4 mg/kg/day
Spironolactone	Children	PO	1.5–3.5 mg/kg/day, divided q6–24h

IM, Intramuscular; IV, intravenous; ND, no data; PO, oral.

Modified from Bestic, M., & Reed, M. (2005). Pharmacology review: common diuretics used in the preterm and term infant. *Neoreviews*, 6, 392.

Diuretic Use in Neonates and Infants

Diuretics represent one of the most common classes of drugs administered to sick neonates. They are primarily used in the treatment of **edema** associated with inappropriate water and sodium retention, such as congestive heart failure, kidney disorders, and liver disease.³⁴

Furosemide is often administered off-label in premature neonates, to also treat respiratory conditions and at doses greater than recommended. Furosemide is used in almost 50% of infants with bronchopulmonary dysplasia and nearly 25% of infants with respiratory distress syndrome and/or transient tachypnea of the newborn.³⁵

Nevertheless, routine or sustained use of aerosolized loop diuretics in infants with (or developing) chronic lung disease cannot be recommended on the basis of existing evidence.³⁶

Furosemide and Fluid Overload

Diuretics are used in the neonatal population for the treatment of several fluid retention states, including renal dysfunction and post-operative management, and during treatment with extracorporeal membrane oxygenation (ECMO). To avoid acute fluctuations in intravascular volume associated with bolus administration of loop diuretics, the use of continuous intravenous administration has been proposed. After cardiac surgery in patients younger than 6 months of age, urinary output can be significantly greater when receiving continuous furosemide compared with intermittent dosing.³⁷

However, compared with continuous dosing, adjustable dosing of furosemide based on clinical parameters can result in higher urine production in the intermittent period and requires a significantly smaller total daily dose of the drug.³⁸

In neonates treated with ECMO, no observed benefit of continuous treatment has been shown in comparison with intermittent furosemide administration.³⁹

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What is a diuretic?
2. Identify the five major groups of diuretics used clinically.
3. If a diuretic agent, such as one of the loop diuretics, causes loss of K⁺, how would this lead to metabolic alkalosis?
4. Which diuretics would preserve K⁺?
5. What is the potential effect of a carbonic anhydrase inhibitor on acid–base balance?
6. Explain how a diuretic, such as furosemide, can be helpful in acute CHF with pulmonary and vascular edema.
7. Which diuretic agent has a vasodilatory effect when used for long-term treatment?
8. In an otherwise healthy adult with mild hypertension, what diuretic agent should be considered the first-line treatment?
9. Which diuretic agent has been successfully used in the management of ARDS?
10. Match each of the following sets of drugs on the left with the most likely interaction on the right.

Gentamicin <i>PLUS</i> furosemide	Hyperglycemia
Hydrochlorothiazide <i>PLUS</i> prednisone	Ototoxicity and nephrotoxicity
Spironolactone <i>PLUS</i> enalapril	Hyperkalemia
Hydrochlorothiazide <i>PLUS</i> carbamazepine	Hyponatremia

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 73-year-old White man presents to the emergency department with a chief complaint of severe dyspnea that began about 8 hours before presentation. The patient's history is significant for long-standing hypertension and coronary artery disease. He had suffered an inferior myocardial infarction in 1995 and had another myocardial infarction of unknown location in 1999. After this, he underwent a coronary artery bypass

CLINICAL SCENARIO—cont'd

graft procedure. His left internal mammary artery was used to bypass the left anterior descending artery, a saphenous vein graft was placed to the posterior descending artery, and a sequential saphenous vein graft was placed to the first and second obtuse marginal arteries.

Cardiac catheterization revealed inferior wall akinesis with global hypokinesis of the remaining walls. His left ventricular ejection fraction was estimated to be 40%. Since his bypass surgery, he has not had any further angina or infarctions, but he has had two admissions for acute pulmonary edema. Both episodes were believed to have been precipitated by medical noncompliance, but this could not be confirmed. At this presentation, the patient again denies chest pain. He states that he began feeling dyspneic the night before presentation and then awoke about 5 AM severely dyspneic and coughing up white, foamy phlegm. When queried about his compliance with his medicines, he admits that he sometimes forgets to take his clonidine.

The patient has chronic renal insufficiency and has had repair of a right inguinal hernia. He denies any allergies.

The patient is taking the following medications: clonidine, 0.1 mg PO bid; atenolol, 50 mg PO hs each night; aspirin, 325 mg PO qid; transdermal nitroglycerin, 0.4 mg qh (he places a patch on in the morning and takes it off at bedtime); and furosemide, 40 mg PO q AM.

Physical examination reveals an elderly White man in obvious respiratory distress. He is afebrile; other vital signs are as follows: pulse (P) 120 beats/min and regular, respiratory rate (RR) 32 breaths/min, and blood pressure (BP) 230/140 mm Hg. His neck shows positive jugular venous distention. Heart auscultation reveals a regular rate, with a systolic ejection murmur (I/VI), negative S₃, and positive S₄. His lungs show bibasilar inspiratory crackles half of the way up the thorax. His abdomen is flat, and bowel sounds are present; no tenderness or masses are identified. His extremities are slightly cool, and pulses are felt in all extremities but are thready.

The patient's laboratory results are as follows: Na⁺ 138 mEq/L, K⁺ 3.6 mEq/L, blood urea nitrogen (BUN) 40 mg/dL, and creatinine 2.8 mg/dL. His electrocardiogram shows sinus tachycardia, with inferior Q waves and lateral Q waves of questionable significance. A chest radiograph shows mild cardiomegaly with bilateral infiltrates consistent with pulmonary edema.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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20

Drugs Affecting the Central Nervous System

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CHAPTER OUTLINE

Neurotransmitters

Psychiatric Medications

Antidepressants

Mood Stabilizers

Antipsychotics

Drugs for Alzheimer Dementia: Cholinesterase Inhibitors

Anxiolytics

Barbiturates

Other Hypnotics

Ethyl Alcohol

Pain Treatment

Nonsteroidal Antiinflammatory Drugs

Opioid Analgesics

Routes of Opioid Administration

Opioid Inhalation

Local Anesthetics

Epidural Analgesia

Combinations of Analgesic Classes

Chronic Pain Syndromes

Anesthesia

Conscious Sedation

Standards for Providing Conscious Sedation

Central Nervous System and Respiratory Stimulants

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms pertaining to drugs that affect the central nervous system (CNS)
2. Describe the multiple functions of the CNS
3. Recognize various effects of medications on the CNS and their abilities to modulate neurotransmitters
4. Comprehend psychiatric medications, including classification, use, and side effect profiles
5. Recognize the effects of alcohol on the CNS during acute intoxication, chronic use, and after abrupt withdrawal
6. Distinguish physiologic and psychological bases of pain and the classes of analgesics used to treat pain
7. Recognize indications for the use of both local and general anesthesia
8. Describe the concept of conscious sedation and indications and guidelines for use
9. Distinguish drugs that stimulate the CNS and respiratory system and describe the indications for application

KEY TERMS AND DEFINITIONS

Analgesics Drugs that provide pain relief. Analgesics can be subdivided into narcotic and nonnarcotic medications. Narcotic drugs are derivatives of opium, such as morphine and codeine. Nonnarcotic medications are useful in treating pain and inflammation. They also have antipyretic activity.

Anesthetics Drugs that depress the central nervous system. Anesthetics can be divided into local and general anesthetics. General anesthesia causes total loss of consciousness and reflexes, which results in the absence of pain perception. Local anesthetics are applied to a specific site and decrease pain perception at the specific site and do not affect level of

consciousness. Both types of anesthetics are often used during surgical procedures.

Antidepressants Drugs that can alter levels of certain neurotransmitters within the brain, in particular norepinephrine and serotonin. Depending on the class of antidepressant, they can either inhibit the reuptake of neurotransmitters or decrease their degradation, ultimately allowing for increased levels of neurotransmitter at the nerve terminal.

Antipsychotics Drugs used to treat psychotic disorders, such as schizophrenia. Antipsychotics primarily affect the neurotransmitter dopamine.

Anxiolytics Minor tranquilizers. Anxiolytics are drugs used to treat several conditions, including anxiety disorders and insomnia. The most common class of anxiolytics is the benzodiazepines. They bind to the γ -aminobutyric acid (GABA) receptor to increase the inhibitory actions of this neurotransmitter.

Central nervous system (CNS) The brain and spinal cord make up the functional components of the CNS. The spinal cord provides nerve fibers that transport signals to and from the brain. The brain largely comprises three components: cortex, midbrain, and brainstem. Together, these provide for all conscious and subconscious functions of the body.

Cholinesterase inhibitors Drugs that block the activity of cholinesterase, an enzyme that inactivates the neurotransmitter acetylcholine. Acetylcholine is found at nerve terminals in both the CNS and the peripheral nervous system. Cholinesterase inhibitors are used in the treatment of dementia to slow the progression of cognitive decline.

Conscious sedation Method used during certain invasive procedures. The goals of conscious sedation are to decrease the level of consciousness and relieve anxiety and pain while allowing the patient to follow verbal commands. Conscious sedation is achieved through the use of several classes of drugs, including benzodiazepines and narcotic analgesics.

Mood stabilizers Drugs used primarily to treat bipolar disorders.

Neurotransmitter Chemical substance that allows neurons to transmit electrical impulses throughout the CNS and the peripheral nervous system. The action of the electrical impulse is determined by the chemical structure of the neurotransmitter and the receptor to which it binds.

Stimulant A drug that increases activity of the brain. Stimulants can be divided into two classes: amphetamines and respiratory stimulants. Amphetamines cause increased wakefulness, improved concentration, and appetite suppression. Respiratory stimulants include doxapram, xanthines, carbonic anhydrase inhibitors, salicylates, and progesterone.

The most widely used drugs, both therapeutic and recreational, are agents affecting the **central nervous system (CNS)**. Humans are intrinsically concerned with and perhaps even defined by the processes of thinking and feeling. These processes originate within the brain. Thoughts and feelings, although poorly understood, reside primarily with neurochemical interactions and balance in the brain. Drugs that affect the CNS are used for their effects on perception and mood. Although the gross anatomy of the brain has been elegantly described, the complex interaction of various brain areas and individual neurons is less well understood.

Generally, the cortex, or outer covering, of the brain is considered to be the location of thought, memory, self-awareness, and personality. Perception of sensation and control of body movement, including speech, are also represented in specific areas of the cortex. The midbrain functions as a relay station for information traveling to and from the cortex. It also integrates and modulates autonomic functions; this function occurs primarily in the hypothalamus. The brainstem, or medulla, contains the control areas for autonomic functions, such as breathing and cardiovascular control, and the area responsible for alertness, the reticular activating system. The spinal cord enters the brain at the brainstem, and the cerebellum, immediately behind the brainstem, affects fine motor control and coordinates movement.

Much of our understanding of brain organization and function comes from removing areas of the brain and identifying the resulting deficits in animals. Some information has been acquired by studying humans who have had strokes or traumatic brain surgery. These observations have led to a general understanding of functional neuroanatomy and recognition that the brain can recover significant function after damage to important areas.

Individual neurons have a wide array of connections with many different neurons in diverse areas of the brain; this is more complicated than the gross anatomy would suggest. These patterns are different in different individuals and change with time in the same individual. Many functions apparently are represented in multiple ways, making them resistant to damage. Although the number of individual neurons does not increase in adulthood, the brain is

able to change and increase the number of connections and complexity of the neuronal circuitry throughout life. Although each neuron releases only a single **neurotransmitter** and occasionally a co-neurotransmitter, the actual effect of these neurotransmitters on the next neuron is modified by additional presynaptic and postsynaptic neurons, which may inhibit or augment the primary neurotransmitter effect.

Several diseases are apparently related to loss of particular neurons with specific neurotransmitters. Parkinson disease is caused by a loss of dopamine-containing neurons in the *substantia nigra* area of the midbrain. This condition is characterized by resting tremor; rigidity; bradykinesia, or slowness in initiating movement; gait disturbances; and postural instability. Treatment of Parkinson disease involves increasing the amount of dopamine contained in and released from the remaining neurons.^{1,2} Some forms of depression are believed to be caused by reduced activity of norepinephrine neurons in the brain, particularly neurons in the *locus caeruleus*.³ There seems to be a decrease in the preganglionic augmentation effects of serotonin and in direct stimulatory effects of norepinephrine. Treatment is to restore more normal activity of the norepinephrine neurons by inhibiting the reuptake of serotonin by modulating neurons, enhancing the amount of norepinephrine released, and increasing the duration of its effects in the synapse.

Because of the diversity of neuronal connections and the plasticity of the CNS, drugs used for CNS therapy have widespread and varying effects. The functional and chemical complexities of the brain and peripheral nervous system explain the occurrence of side effects and toxicities common with CNS drug therapy.

KEY POINT

Drugs that affect the central nervous system (CNS) are commonly prescribed. These drugs exert their effects by interacting with neurotransmission; by affecting neurotransmitter release, metabolism, or uptake; or by acting at primary or modifying receptors or transport proteins.

Neurotransmitters

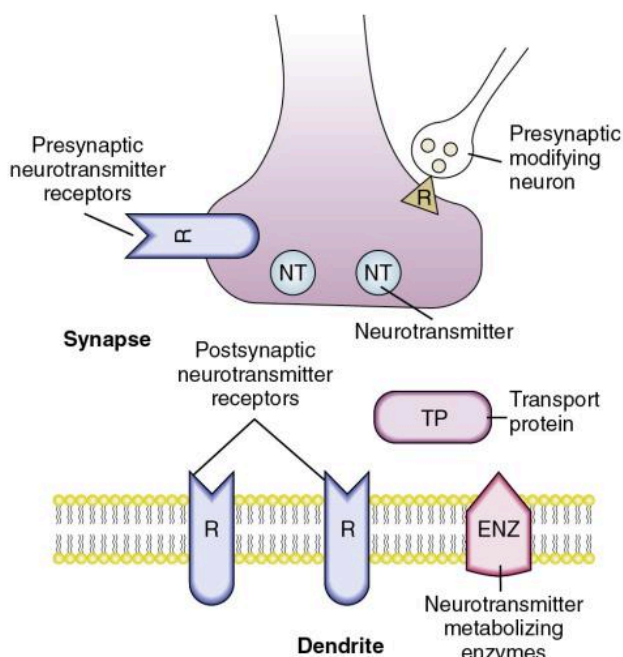
KEY POINT

Because the organization of the central nervous system (CNS) is complex, the main cause of the side effects of CNS drugs is their interaction in diffuse areas of the brain.

KEY POINT

Central nervous system (CNS) drugs may increase or decrease individual neuronal activity. The balance of activity of different types of neurons seems to affect brain function and mood. Restoration of this balance is the goal of treatment of mood disorders.

Each neuron releases predominantly one type of neurotransmitter from its axon. If enough receptors are activated on the postsynaptic membrane, electrical depolarization occurs and a signal is passed to the next neuron. The functional anatomy and components of neurotransmission are illustrated in Figs. 20.1 and 20.2. Released neurotransmitters are bound to and transported by proteins in the synapse, taken back up by the releasing nerve terminal, repackaged into vesicles, and recycled. Bound neurotransmitters are unavailable for receptor interactions, and alterations in the transport proteins in amount or affinity affect the signal propagation potential. Some of the released neurotransmitter is metabolized by membrane-bound enzymes on the postsynaptic cell membrane. The resulting constituent components are taken up presynaptically and used as precursors for neurotransmitter synthesis. Receptors on both the presynaptic membrane and the postsynaptic membrane specific for the released chemicals and for other chemicals from modulating and neighboring neurons affect the activity of the neuron.



• **Fig. 20.1** Schematic of components of neuron-to-neuron communication. Neurotransmitter (NT) is synthesized in the nerve and transported and stored in the nerve terminal. Other components of neurotransmission include transport proteins (TP) in the synapse, receptors (R) on the postsynaptic membrane, receptors (R) on the presynaptic membrane, membrane-bound enzymes (ENZ), and modifying neurons.

Chemicals that behave as neurotransmitters are listed in Table 20.1. The effect of the neurotransmitter released is determined by many factors, including the amount of neurotransmitter released, type and quantity of transport proteins, previous release of neurotransmitters, presence of modifying substances, efficiency of reuptake processes, and activities of modulating interneurons. Specifics of this transmission modulation system differ for various brain areas, mental functions, and neurotransmitters. CNS-active drugs may have effects on specific parts of a neurotransmitter system or have generalized effects on brain function. Augmentation or inhibition of neurotransmission can result from drug interaction at any of the sites illustrated in Figs. 20.1 and 20.2.

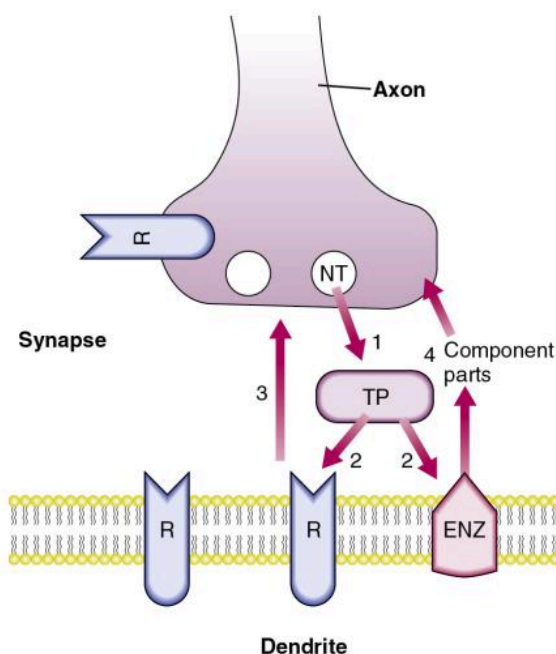
Psychiatric Medications

KEY POINT

Depression is a common mood disorder. Several classes of drugs, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs), are used for this disorder and exhibit a wide range of side effects.

Antidepressants

Depression is one of the most common psychiatric disorders and a major cause of worldwide disability. In the United States, the estimated major depression prevalence is 7.8%.⁴ An estimated 322 million people globally (4.4% of the world's population) currently live with depression.⁵ The prevalence of major depressive disorder has also increased by 18.4% worldwide from 2005 to 2015.⁵ In fact,



• **Fig. 20.2** Schematic for pathways that neurotransmitters follow after release into the synapse. After axonal depolarization, stored neurotransmitter (NT) is released into the synapse (1), where it is bound to the transport or carrier protein (TP). NT is transported to and binds with postsynaptic receptors (2), is metabolized by membrane-bound enzymes (2), is actively taken up by the releasing neuron (3), or is released and binds to presynaptic receptors. NT substance that is degraded to its component parts is taken up by the releasing neuron to be resynthesized and reused (4).

TABLE 20.1 Central Nervous System Chemicals That Function as Neurotransmitters

Chemical Class	Neurotransmitter
Biogenic amines	Norepinephrine
	Epinephrine
	Dopamine
	Acetylcholine
	Histamine
	Serotonin (5-hydroxytryptamine)
Amino acids	γ -Aminobutyric acid (GABA)
	Glutamate
	Glycine
	Aspartate
Nucleotides and nucleosides	Adenosine triphosphate
	Adenosine
Peptides	Thyrotropin-releasing hormone
	Enkephalins
	Angiotensin II
	Oxytocin
	Vasopressin
	Bradykinin
	Dynorphin
	Substance P
	Substance K
	Neuropeptide Y
	β endorphin
	Luteinizing hormone–releasing factor
	Corticotropin-releasing factor
	Somatostatin
	Secretin
	Melanocyte-stimulating hormone

mental disorders overall now account for 4.9% of all Disability-Adjusted Life Years (DALYs).⁶

Depressive disorder has multiple etiologies, including biologic, psychological, and social factors. Serotonin and norepinephrine have been shown to be important neurotransmitters, and their relative deficiency has been linked to depression. For more than a decade, *selective serotonin reuptake inhibitors (SSRIs)* have been the first-line medical treatment for major depressive disorder. These drugs are preferred because they are safer and more tolerable than older medications, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In addition, newer drugs target both norepinephrine and serotonin; they are called *serotonin norepinephrine reuptake inhibitors*. Depressive disorder agents are listed in [Table 20.2](#).

Mood Stabilizers

Mood stabilizers are used primarily for bipolar disorder. This affective disorder involves alternating episodes of depression and mania or hypomania. Mania is characterized by at least 1 week of elevated or irritable mood and at least three of the following: inflated self-esteem or grandiosity, decreased need for sleep, being more talkative than usual, rapid thoughts or the subjective experience that one's thoughts are racing, distractibility, an increase in goal-directed behavior, or excessive involvement in pleasurable activities that have a high potential for painful consequences.⁷ Hypomania is similar to mania but less intense and of shorter duration.⁷

Medical treatment of any degree of bipolar disorder must begin with a mood stabilizer. These drugs include lithium; anti-convulsants, such as valproic acid, carbamazepine, gabapentin, and lamotrigine; and **antipsychotics**, which are discussed subsequently. Except for lithium, the main side effect of these drugs is sedation. Lithium has a narrow therapeutic window and consequently must be used judiciously. Lithium can cause tremor, cognitive slowing, hypothyroidism, renal insufficiency, leukocytosis, polyuria, and polydipsia. Lithium toxicity can result in coma.⁸ [Table 20.3](#) lists common mood stabilizers.

Antipsychotics

Psychotic disorders are characterized by impaired reality testing. They include schizophrenia spectrum disorders and psychosis associated with depression or mania. Pharmacotherapy is generally used to increase dopamine in the brain. These drugs are most efficacious for active psychotic symptoms, such as hallucinations and abnormal thought processes. Older drugs, such as thiorazine, thioridazine, and haloperidol, had numerous side effects, which affected compliance. These side effects included extrapyramidal symptoms, such as cogwheel rigidity, acute dystonia, oculogyric crisis, and cholinergic side effects. Newer agents, such as risperidone, olanzapine, and quetiapine, are more tolerable. [Table 20.4](#) lists common antipsychotics.

Drugs for Alzheimer Dementia: Cholinesterase Inhibitors

Alzheimer dementia is associated with cognitive deficits secondary to decreased acetylcholine levels within the brain. **Cholinesterase inhibitors** may improve cognition and function in patients with Alzheimer disease. These drugs include donepezil, tacrine, galantamine, and rivastigmine. The use of these drugs is sometimes limited by gastrointestinal side effects, which include nausea, vomiting, diarrhea, and hepatotoxicity, especially with tacrine.⁹ These drugs are listed in [Table 20.5](#).

Anxiolytics

KEY POINT

β -aminobutyric acid (GABA) channel activation may also be important in the production of general anesthesia and sleep. Sleep is a complex activity, and induction of sleep can be pharmacologically influenced by sedative drugs; however, the quality of sleep induced by sedative drugs is poor.

CLINICAL CONNECTION

Antagonism of the benzodiazepine receptor site can be accomplished with use of flumazenil, which binds to the receptor site but does not activate the receptor.

Benzodiazepines are agents that have been used to reduce anxiety under a variety of circumstances. **Anxiolytics** are also used as amnestics, preventing conversion of short-term experience into permanent memory. By themselves, they cause no change in respiration; however, these agents may augment the respiratory depression induced by opioids. They have little effect on cardiac function and are very safe agents from this standpoint. Benzodiazepines are excellent induction agents when providing general anesthesia and are useful in preventing unpleasant recall during uncomfortable

TABLE 20.2 Drugs Used to Treat Depression

Class	Generic Drug	Brand Name
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	Celexa
	Fluoxetine	Prozac
	Olanzapine and Fluoxetine	Symbyax
	Fluvoxamine Maleate	Luvox
	Paroxetine	Paxil, Paxil CR, Pexeva, Brisdelle
	Sertraline	Zoloft
Serotonin and norepinephrine reuptake inhibitors	Escitalopram oxalate	Lexapro
	Venlafaxine	Effexor XR
	Duloxetine	Cymbalta, Drizalma
Serotonin receptor antagonist	Desvenlafaxine	Pristiq
	Nefazodone	Generic
Dopamine reuptake inhibitor	Bupropion	Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL
Dopamine reuptake inhibitor and opioid antagonist	Bupropion and Naltrexone	Contrave
Tricyclic antidepressants (TCAs)	Amitriptyline	Generic
	Amoxapine	Generic
	Clomipramine	Anafranil
	Desipramine	Norpramin
	Doxepin	Silenor, Zonalon
	Imipramine	Tofranil
	Nortriptyline	Pamelor
	Protriptyline	Generic
	Trimipramine	Generic
Monoamine oxidase inhibitors (MAOIs)	Mirtazapine	Remeron, Remeron SolTab
	Phenelzine	Nardil
	Tranylcypromine	Parnate
Herbal remedy	Isocarboxazid	Marplan
	St. John's wort (<i>Hypericum perforatum</i>)	St. John's wort
Miscellaneous drugs	Trazodone	Desyrel

CR, Controlled release; SolTab, orally disintegrating tablet; SR, sustained release (12 hour); XL, extra long (extended release 24 hour); XR, extended release.

TABLE 20.3 Drugs Used as Mood Stabilizers

Generic Drug	Brand Name
Carbamazepine	Tegretol, Tegretol-XR, Eptol, Carbatrol, Equetro, Teril
Lamotrigine	Lamictal, Lamictal XR, Lamictal CD, Lamictal ODT
Lithium	Lithobid, Eskalith
Valproic acid	Generic

CD, Chewable; XR, extended release; ODT, orally disintegrating.

interventions. They may be used as somnifics. These agents are used to terminate seizures, and they elevate seizure threshold. Benzodiazepines exert their effects by binding to benzodiazepine receptors in the γ -aminobutyric acid (GABA) receptor complex on neurons, increasing the GABA chloride channel permeability, which hyperpolarizes the neuron, making depolarization less

likely (Fig. 20.3). A specific antagonist, flumazenil (Romazicon), can reverse the sedative effects of the benzodiazepines.

Several other drugs are used to treat anxiety and insomnia. Some of these are listed with the benzodiazepines in Table 20.6. Their mechanisms of action are not related to interactions with the benzodiazepine receptor or the GABA system. Some of the drugs listed in Table 20.6 are used to promote sleep; these and other nonrelated sleep-inducing agents are listed in Table 20.7. Although they induce sleep, benzodiazepines and other drug classes interfere with the normal sleep cycles by reducing the amount of time spent in rapid eye movement (REM) sleep.

Barbiturates

The barbiturates, one of the oldest groups of sedative drugs, are derived from barbituric acid. Because of their toxic potential and rapid development of tolerance, barbiturates have largely been replaced by benzodiazepines except for a few specialized uses. Ultra-short-acting barbiturates are used for anesthetic induction (thiopental, thiamylal, and methohexital), as hypnotics (pentobarbital and secobarbital),

TABLE 20.4 Drugs Used in Management of Psychotic Disorders

Class	Generic Drug	Brand Name
Phenothiazines	Chlorpromazine	Generic
	Fluphenazine	Generic
	Perphenazine	Generic
	Prochlorperazine	Compro, Procomp
	Trifluoperazine	Generic
Perphenazine and Tricyclic antidepressant	Perphenazine and Amitriptyline	Generic
Thioxanthene	Thiothixene	Generic
Butyrophenones	Droperidol	Inapsine
	Haloperidol	Haldol
Miscellaneous agents	Clozapine	Clozaril, Versacloz
	Lithium	Lithobid
	Olanzapine	Lybalvi, Zyprexa, Zyprexa Zydis, Zyprexa Relprevv
	Pimozide	Generic
	Quetiapine	Seroquel, Seroquel XR
	Risperidone	Perseris, Risperdal, Risperdal Consta
	Ziprasidone	Geodon
	Aripiprazole	Abilify, Aristada
	Paliperidone	Invega, Invega Hafyera, Invega Sustenna, Invega Trinza
	Iloperidone	Fanapt

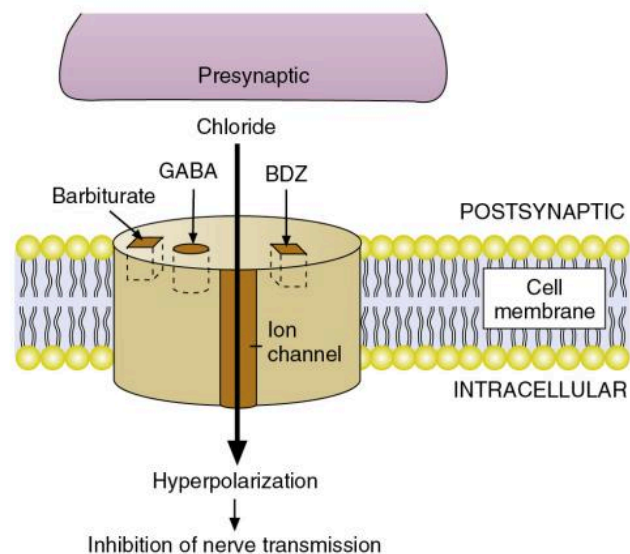
ODT, Orally disintegrating; XR, extended release.

TABLE 20.5 Drugs Used in Treatment of Dementia

Class	Generic Drug	Brand Name
Cholinesterase inhibitors	Donepezil	Aricept
	Galantamine	Razadyne ER
	Rivastigmine	Exelon
	Memantine	Namenda, Namenda XR
	Donepezil and Memantine	Namzaric

ER, XR, Extended release

and for seizure control and prophylaxis (phenobarbital). Use of barbiturates as hypnotics is limited by rapid development of tolerance and reduction in the quality of sleep (decreased amount of REM sleep). They are potent inducers of the cytochrome P450 (CYP) drug-metabolizing system that can alter the levels of many other drugs. Although many of the therapeutic effects of barbiturates are mediated by a specific receptor at the GABA-mediated inhibitory receptor, they have widespread depressive effects on neuron activity. Intentional or accidental overdose results in respiratory arrest and cardiovascular collapse because of depression of the brain control center. This drug class also carries a high risk of addiction and abuse. Severe withdrawal symptoms, including seizures, occur after abruptly stopping long-term use of barbiturates.



• **Fig. 20.3** Mode of action by which barbiturates and benzodiazepines (BDZ) depress central nervous system function; stimulation of receptors on the chloride ion channel facilitates γ -aminobutyric acid (GABA)-induced inhibition of neuronal function.

TABLE 20.6 Drugs Used to Treat Anxiety and Insomnia

Class	Generic Drug	Brand Name
Benzodiazepines	Alprazolam	Xanax, Xanax XR
	Clorazepate dipotassium	Tranxene
	Chlordiazepoxide	Librium, Librax
	Diazepam	Valium, Diastat, Valtoco
	Estazolam	Generic
	Flurazepam	Flurazepam
	Lorazepam	Ativan, Loreev XR
	Midazolam	Seizalam, Nayzilam
	Oxazepam	Generic
	Temazepam	Restoril
	Triazolam	Halcion
Benzodiazepine antagonist	Flumazenil	Generic
Other anxiolytics	Buspirone hydrochloride	Generic
	Doxepin hydrochloride	Silenor, Zonalon
	Hydroxyzine	Vistaril
	Meprobamate	Meprobamate

XR, Extended release.

Other Hypnotics

Difficulty sleeping is a common clinical complaint that frequently results in the prescription of a hypnotic. In addition to the short-acting benzodiazepines and barbiturates mentioned earlier, several other sedatives are used for inducing sleep. All of these agents disrupt sleep patterns and may not improve overall well-being. Hypnotics to induce sleep are generally recommended for brief periods (1 or 2 weeks). However, some patients continue to take these medications for years. A new drug, eszopiclone, is approved for long-term use. Medications used for sleep enhancement are listed in [Table 20.7](#).

TABLE 20.7 Medications Used to Induce Sleep

Class	Generic Drug	Brand Name
Benzodiazepines	Estazolam	Generic
	Flurazepam hydrochloride	Generic
	Quazepam	Doral
	Temazepam	Restoril
	Triazolam	Halcion
Barbiturates	Pentobarbital	Nembutal
Antihistamines	Cyproheptadine	Cyproheptadine
	Diphenhydramine	Benadryl
	Hydroxyzine	Vistaril
Miscellaneous	Dexmedetomidine	Precedex
	Ethanol (alcohol)	
	Eszopiclone	Lunesta
	Ramelteon	Rozerem
	Zaleplon	Sonata
	Zolpidem	Ambien, Ambien CR, Edluar

CR, Controlled release.

Ethyl Alcohol

Alcohol is a by-product of sugar fermentation. It is used as a socially acceptable nonprescription, sedative–hypnotic agent. Ingested to excess, alcohol behaves like a general anesthetic by depressing all brain areas, resulting in loss of voluntary muscle control and consciousness. At toxic levels (400 to 600 mg/dL blood alcohol level), the respiratory center is affected and death as a result of respiratory arrest is likely. The disinhibiting effects of modest alcohol intoxication result from depression of higher cortical behavior control centers, probably by decreasing the GABA receptor effects of endogenous mediators. At higher levels, diffuse membrane-disruptive effects occur, causing generalized neurologic depression. When combined with other sedative–hypnotic drugs, the degree of intoxication is additive.

Chronic alcohol ingestion results in upregulation of GABA receptors and other brain functions, with the development of tolerance to the intoxicating and toxic depression caused by alcohol. Abrupt withdrawal after prolonged use may result in the syndrome of *delirium tremens* (DTs), characterized by CNS hyperactivity, including hyperthermia, increased blood pressure, muscle twitching, hallucinosis, and seizures. The mortality from DTs is high, ranging from 5% to 10% if seizures occur. The withdrawal syndrome can be prevented or treated with any of the sedative–hypnotic drugs; usually a benzodiazepine is chosen because of its relative safety.

Alcohol is a carbohydrate, and if ingested in large quantities, it replaces many of the dietary calories and decreases appetite. Protein, fat, and vitamin malnutrition are often seen with chronic alcohol abuse. Alcohol is metabolized to carbon dioxide (CO₂) and water (H₂O), producing acetaldehyde in the process. Because it is a food, ethyl alcohol saturates the metabolic enzyme system and undergoes first-order elimination kinetics. This means that a constant amount of alcohol is removed per unit of time, rather than a fixed percentage of the blood concentration as with most

other drugs. In the average person, this results in about 10 to 12 g of alcohol removed per hour.

Pain Treatment

Pain is common in humans. Because pain is a subjective, unpleasant experience, it is difficult to observe and quantitate objectively. Recognition of the physiologic and psychological consequences of inadequate pain treatment has led to increased attention to pain control in patients. In hospitalized patients, estimation of pain has been elevated to the level of a vital sign, on par with blood pressure, heart rate, respiratory rate, and temperature. Pain is now often referred to as the *fifth vital sign*.

Besides the difficulty of estimating the amount of pain, many factors alter patient responses to a given degree of discomfort. Physiologic, social, and psychological factors profoundly alter patient perception and tolerance of pain.^{10,11} The meaning of pain to the individual can affect the reported pain and the response of the pain to treatment. It is helpful to view the pain experience as being composed of at least two components: (1) the sensation of *pain* as mediated by the CNS receiving nociceptive input from peripheral pain receptors and (2) *suffering*, the negative, personal emotional response to the pain experience. The integration and expression of these two components produce the pain behavior, which influences the patient's analgesic requirements. Medications may be directed at the origin, integration, or interpretation of the pain experience. Combinations of medications often are more effective than a single approach to this common problem.

Nonanalgesic drugs also affect perception and tolerance of pain. Sedative drugs, such as the barbiturates and benzodiazepines, seem to reduce pain tolerance—increasing the amount of pain perceived and reported by patients receiving them. This effect probably occurs by reducing cortical modulation of the pain perception, increasing pain behaviors. These agents, when combined with **analgesics**, however, seem to decrease the painful experience and enhance analgesia. When interviewed after resolution of the pain episode, patients do not usually report having experienced pain of the extreme magnitude that was perceived by caregivers.

Another factor that must be taken into account when assessing pain is that patients have poor pain memories. With time, the ability to recall the severity and characteristics of pain diminishes; this applies to the effects of treatment as well. Patients asked whether past pain treatment was effective almost always report improvement in pain, even if objective evaluation at the time documents no change or even worsening pain.¹² **Antidepressants** combined with analgesics are used to treat chronic pain states. These agents may be effective by modifying the depressed mood that accompanies chronic discomfort.

Although there are external clues to the presence and magnitude of a person's pain, personal reports are the only way to judge the presence and magnitude of pain. Visual or numeric analog pain scales are the most commonly employed methods for estimating the magnitude of pain. The simplest and most common pain scale employed is an 11-point scale, with 10 being the worst imaginable pain and 0 being totally without pain. Patients are asked to rate their pain from the worst imaginable pain (10) to no pain at all (0). These scales seem to have internal and external validity.^{13–15} The numeric rating is convenient and recognizable, and it lends itself to frequent repetition and consistent reporting. In children, a series of smiling and frowning faces, such as the Wong/Baker Rating Scale, may be used to allow the child to report the degree of pain.¹⁶ These scales help in assessing the adequacy of analgesia and create a shorthand way for patients to communicate their need for additional analgesia to the bedside caregiver.

Caregivers must integrate visual or numeric analog pain scale reports, patient pain behaviors, and vital signs with their own biases¹⁷ regarding the degree of pain that should be present to decide whether to administer additional analgesic drugs.¹⁸ Caregivers apparently often deliver inadequate amounts of analgesics.¹⁹ Inappropriate expectations in both the patient and the caregiver regarding the degree of pain contribute to this reluctance to administer potent analgesics. Acute pain remains undertreated in many patients.

Nonsteroidal Antiinflammatory Drugs

KEY POINT

Pain may be relieved by nonsteroidal antiinflammatory drugs (NSAIDs), which modify peripheral inflammation and central integration; by opiates, which modify the spinal cord transmission, brainstem processing, and cortical perception of pain; and by local anesthetics, which block sensory transmission.

Nonsteroidal antiinflammatory drugs (NSAIDs) are analgesics frequently used to treat moderate pain (Table 20.8). NSAIDs work by affecting the hypothalamus and by inhibiting the production of inflammatory mediators, primarily prostaglandins, at the peripheral site of the painful stimulus. The salicylates are the oldest member of this class and have been known for more than 100 years for their effects as antipyretics. Aspirin, a salicylate, is a common component of over-the-counter (OTC) analgesics and cold remedies. Aspirin decreases the synthesis of prostaglandin by irreversibly inhibiting two enzymes: cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2). COX-1 is located primarily on tissues, including the blood vessels, the kidneys, and the gastric mucosa, and COX-2 is associated primarily with inflammation. In contrast to aspirin, other drugs, such as ibuprofen and naproxen, reversibly inhibit these enzymes. Although selective COX-2 inhibitors are thought to cause fewer gastrointestinal side effects, there are no clinical trials clearly showing this.²⁰

CLINICAL CONNECTION

Febrile children should not be given aspirin because of the risk of Reye syndrome.

Gastric irritation and ulceration are major problems with administering NSAIDs. Renal injury can result from prolonged use and high doses of these medications. NSAIDs also inhibit platelet aggregation, and this compounds the problem of gastrointestinal bleeding. The antiplatelet effects are used therapeutically either after or to prevent cardiac thrombosis. Aspirin use in childhood febrile illness has been associated with an increased incidence of Reye syndrome, an often fatal increase in intracranial pressure associated with massive hepatic dysfunction.^{21,22} Allergic reactions to NSAIDs are common. Rashes, urticaria, angioneurotic edema, asthma, and anaphylaxis have been reported.

Acetaminophen (Tylenol), although a weak inhibitor of the COX system, has no significant antiinflammatory effects but is effective in relieving mild to moderate pain. It does not inhibit platelets or cause gastric ulcers. In large doses, acetaminophen can cause lethal hepatic necrosis. Because it is used in many nonprescription cold preparations, accidental overdose from combining medications during self-medication occasionally occurs. An overdose of acetaminophen can be treated with oral *N*-acetylcysteine, as described in Chapter 9.

TABLE 20.8 Nonsteroidal Antiinflammatory Drugs

Class	Generic Drug	Brand Name
Nonspecific Cyclooxygenase Inhibitors		
Salicylates	Aspirin	Bayer
	Choline salicylate	Arthropan
	Diffunisal	Diffunisal
	Magnesium salicylate	
	Salsalate	Amigesic, Disalcid
	Sodium salicylate	
Aniline derivative	Acetaminophen [†]	Tylenol
Indoles	Etodolac	Generic
	Indomethacin	Indocin
	Sulindac	Generic
Propionic acid derivatives	Ibuprofen	Advil
	Fenoprofen	Nalfon
	Flurbiprofen	Ansaid
	Ketoprofen	Generic
	Naproxen	Aleve, Anaprox, Anaprox DS, Naprelan, Naprosyn, EC-Naprosyn
	Oxaprozin	Daypro
Piroxicam derivative	Piroxicam	Feldene
Miscellaneous	Diclofenac	Cambia, Cataflam, Zipsor, Zorvolex, Pennsaid
	Ketorolac	Acular, Acular LS, Acuvail, Omidria, Sprix
	Mefenamic acid	Ponstel
	Nabumetone	Generic
	Ziconotide	Prialt
	Mesalamine	Generic
COX-2 Inhibitors		
	Celecoxib	Celebrex, Elyxyb
	Meloxicam	Anjeso, Mobic
	Rofecoxib	Vioxx [*]
	Valdecoxib	Bextra [†]

COX-2, Cyclooxygenase-2; SR, sustained release; XR, extended release.

^{*}Manufacturer voluntarily withdrew agent from the market.

[†]US Food and Drug Administration removed April 7, 2005.

^{*}Not an NSAID, placed for ease of presentation

COX-2 inhibitors have been reevaluated for their potential to cause adverse cardiovascular events. Rofecoxib (Vioxx) and valdecoxib (Bextra) have been withdrawn from the market. Other COX-2 inhibitors are currently undergoing trials to assess their potential to increase cardiovascular risk.

Opioid Analgesics

CLINICAL CONNECTION

Depression of respiratory drive is an important side effect of several classes of central nervous system (CNS) drugs, including general anesthetics and opioid analgesics.

CLINICAL CONNECTION

Opiate effects can be antagonized with an opiate antagonist, with the most commonly used being naloxone.

CLINICAL CONNECTION

Narcan is the only nasal form of naloxone approved by the US Food and Drug Administration (FDA). This agent is available without prescription.

Opioids or narcotic analgesics are derivatives of the naturally occurring drug mixture opium, derived from the poppy plant, *Papaver somniferum*. These agents are used for the treatment of moderate to severe pain. They act by binding to opioid receptors in the brain and spinal cord. They modify pain pathways at the spinal level and profoundly influence the subjective response to pain at the cortical level. Endogenously occurring opioids, the endorphins and enkephalins, are neuromodulators affecting pain perception and mood. Opioids exert their effects and side effects by binding to receptors for these naturally occurring substances.

There are at least three distinct opioid receptors—*mu* (μ), *kappa* (κ), and *delta* (δ)—and several subtypes. Agonist drugs may bind at one or more of these receptors, accounting for some of the differences seen in their effects. Besides pain relief, high enough doses of opioids can result in loss of consciousness and, because of a profound dose-dependent depression of respiratory drive, respiratory arrest. Opioids produce a euphoric effect on mood, making them popular drugs of abuse. Tolerance develops rapidly, and withdrawal is very painful and unpleasant. These factors contribute to the highly addictive potential of the opioids.

The μ receptor is responsible for the analgesic effects in the CNS and spinal cord. It also accounts for respiratory depression, constipation, nausea and vomiting (from the chemotactic trigger zone receptors), and antitussive effects. The κ receptors are located in the spinal cord and, to a lesser extent, in the CNS mediate analgesia. They may be the receptors responsible for the analgesic effects of the mixed agonist–antagonist drugs. The δ receptor is the receptor for the naturally occurring mediator enkephalin; its role in analgesia is unclear. It may be important in the spinal mediation of pain perception. This is just the outline of the opioid receptor system; there are other types and subtypes of receptors. Their actual function in human health is not understood. The effect of various opioids can be explained by their actions at one or more of these receptors.

Opioids are listed in Table 20.9. Some have pure agonist effects, acting as the endogenous mediators at the receptors, and others antagonize the endogenous mediators but have a small agonist effect (mixed drugs or agonist–antagonist drugs). There are several strictly antagonist agents. These drugs are used to reverse the analgesic and respiratory depressive effects of the opioids. Recently, Narcan (naloxone) nasal spray has been approved for use to combat the high incidence of opioid overdoses in the United States. In many states, Narcan can be purchased without a prescription. The most serious side effect of an opioid agonist is respiratory depression, which is mediated by decreased sensitivity of the respiratory center to elevations in partial pressure of arterial carbon dioxide (PaCO_2). Miosis (small pupils) is pathognomonic for opioid drug administration and is a consequence of the effects on the sympathetic nervous system. Constipation results from opioid depression of motility of the stomach and intestines. Nausea and vomiting are a direct effect on the

TABLE 20.9 Opioid Drugs

Effect at Opioid Receptor	Generic Drug	Brand Name
Agonist	Morphine	Apokyn, Duramorph PF, Infumorph, Kynmobi, Mitigo, MS Contin
	Opium	Paregoric
	Codeine	Numbrino
	Alfentanil	Alfenta
	Dihydrocodeine	Available only in combination with other agents
	Fentanyl	Fentora, Lazanda, Sublimaze, Subsyst, Actiq
	Heroin	—
	Hydrocodone	Available only in combination with other agents
	Hydromorphone	Dilaudid
	Levorphanol	Generic
	Meperidine	Demerol
	Methadone	Generic
	Oxycodone	Oxaydo, Roxicodone, OxyContin, Xtampza ER
	Oxymorphone	Oxymorphone
	Remifentanyl	Ultiva
	Sufentanil	Dsuvia, Sufenta
	Tramadol	Conzip, Qdolo, Seglantis, Ultracet, Ultram
Mixed agonist-antagonist	Buprenorphine	Belbuca, Butrans, Buprenex, Sublocade, Suboxone, Zubsolv
	Butorphanol	Generic
	Nalbuphine	Generic
	Pentazocine	Available only in combination with other agents
Antagonist	Naloxone	Kloxxado, Narcan, Zimhi
	Naltrexone	Vivitrol
	Methylnaltrexone	Relistor

ER, Extended release; MS, morphine sulfate.

brainstem effectors. Cough suppression results from a direct central effect of the opioid.

Because of their effects on pain perception, narcotics are often used as part of a balanced anesthetic. Doses that cause profound depression of respiration have minimal or no effect on cardiac function; because of this, opioids are the basis for anesthesia for patients with serious cardiovascular compromise. By themselves, opioids have no effect on consciousness or memory. Combined with small doses of benzodiazepines or gaseous anesthetics, they can be used to provide surgical anesthesia.

Strong opioid drugs are often referred to as *narcotics*, from the Greek word for stupor. The word *narcotic* has significant legal overtones. For this reason, its use has been avoided in this section. *Opiates* are compounds derived from opium and represent a small number of the drugs discussed in this section. The term *opioids*, as used in this section, implies simply that the agents interact with one or more of the opioid receptors.

Routes of Opioid Administration

KEY POINT

Inadequate pain relief has been identified as a serious problem. Many pain control options are available to hospitalized patients.

KEY POINT

Patient-controlled (opioid) analgesia (PCA), epidural analgesia with local anesthetics and opioids, and combinations of analgesic classes can result in excellent postoperative pain relief.

CLINICAL CONNECTION

For patients who require patient-controlled analgesia (PCA), a bag-mask and naloxone should be available in the room at all times.

As discussed previously, pain is a subjective experience. Inadequate analgesia is a common complaint voiced by patients and is especially a problem after surgery. Fear of respiratory depression is often given as the reason caregivers are reluctant to administer more opioids. Novel ways of treating pain have been developed to improve treatment of pain. Patient-controlled analgesia (PCA) is a method by which patients can self-administer a predetermined intravenous bolus of an opioid at a set interval. Use of PCA avoids the delay in getting a dose requested from and later delivered by a nurse.

Opioid Inhalation

CLINICAL CONNECTION

Nebulized opioids may be used to treat dyspnea.

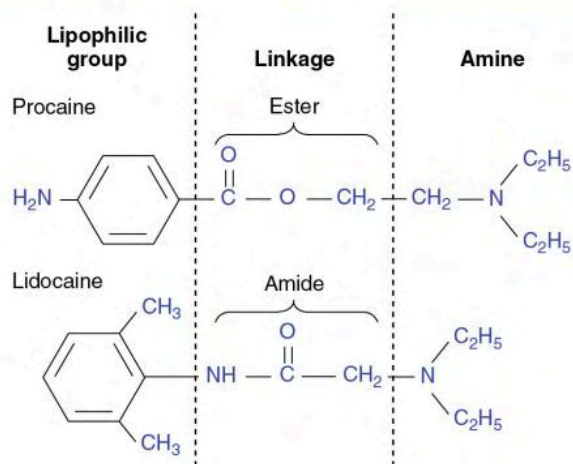
Opioids are occasionally administered via inhalation. Inhaled opioids have been suggested to be more effective than systemic opioids for decreasing the sensation of dyspnea in patients with advanced respiratory failure. Opioid receptors have been found in lung tissue, but their exact function in modifying the sensation of dyspnea has not been determined. Inhaled (nebulized) opioids may affect dyspnea by a central mechanism because these drugs are rapidly absorbed from the lung. No controlled studies have shown improved effectiveness of opioids when administered via inhalation; however, this route may be an alternative when intravenous access is unavailable.²³ Patients with terminal cancer without lung disease have been given systemic doses of analgesics through this route, with good clinical effect achieved.

Local Anesthetics

KEY POINT

Local anesthetics block sodium channels in the axons and abolish neural transmission.

Pain treatment can be achieved by blocking transmission of the pain impulse from the damaged area. Local anesthetics are used to interrupt these neurologic signals. Local anesthetics produce nerve conduction block by blocking sodium channels. These are located all along the cell, including the axon. When depolarization occurs, the impulse is propagated down the axon by an abrupt increase in the membrane sodium permeability. When the drug binds to and



• **Fig. 20.4** Chemical structures of local anesthetics procaine and lidocaine, showing their respective ester and amide linkages, location of the lipophilic group, and ionizable amine group.

TABLE 20.10

Examples of Local Anesthetics

Class	Generic Drug	Brand Name
Esters	Benzocaine	Hurricane, Solarcaine
	Chloroprocaine	Clorotekal, Nesacaine, Nesacaine-MPF
	Procaine	Available only in combination with other agents
Amides	Bupivacaine	Exparel, Marcaine, Sensorcaine, Zaracoll, Zynrelef
	Lidocaine	Akten, Glydo, Xylacaine, Lidoderm, Zingo, Ztldo
	Mepivacaine	Carbocaine, Isocaine, Polocaine, Polocaine-MPF, Scandonest L, Scandonest Plain
	Prilocaine	Citanest Forte Dental
	Ropivacaine	Naropin

occludes the channel pore, sodium is unable to enter the cell, and propagation of the electrical impulse is stopped. All local anesthetics consist of a lipophilic part and a hydrophilic, amine part connected by either an amide or ester linkage; this is illustrated in Fig. 20.4. Table 20.10 lists several common agents. Sodium channel blockade makes some of these drugs useful in terminating cardiac conduction abnormalities in addition to providing analgesia. Some evidence suggests that systemic administration or inhalation may also enhance bronchodilation in asthma and suppress irritant tracheal cough responses. At toxic levels, CNS excitation occurs, and frank seizures may result. Epinephrine is often added to a local anesthetic for vasoconstriction to delay its absorption, prolonging its effect and decreasing blood levels and potential toxicity. Bupivacaine is very cardiotoxic, and a toxic dose may result in profound and prolonged cardiac depression or arrest.

Epidural Analgesia

Continuing epidural infusions for analgesia have improved postoperative pain therapy. There is evidence that patient outcome

may also be improved with epidural infusions of local anesthetics, opioids, or both^{24,25}; this is especially true for very ill patients.^{26–29} The quality of analgesia and the ability to eliminate pain in many body areas are superior with local anesthetic infusion compared with systemic analgesics. Epidural infusions are common in some surgical procedures, especially in the delivery of newborns via cesarean section. Minimal effects on normal sensory and motor function can be achieved with very dilute local anesthetics. Addition of opioids to the mixture permits even less local anesthetic to be infused. If sympathetic blockade produces unacceptable hypotension, local anesthetics can be eliminated completely, with significant analgesia obtained with opioid infusion alone. Pain modulation from epidural opioids occurs at receptors at the spinal cord segmental level. The major side effects of epidural analgesia with use of local and opioid infusions are listed in [Box 20.1](#).

Combinations of Analgesic Classes

Another strategy to improve analgesia and to reduce the likelihood of opioid overdose is to combine several different classes of analgesics. Prescription combinations of NSAIDs and opioids are widely available ([Table 20.11](#)). The concept of attacking pain at several places is useful, but the fixed combinations of drugs with different effects, toxicities, and half-lives make titration to an individual patient's needs difficult with these agents. Use of the separate agents, independently titrated, may improve this problem, but it is more difficult for patients to take numerous medications.

• BOX 20.1 Side Effects of Agents Used for Epidural Analgesia

Local Anesthetics

- Motor weakness
- Numbness
- Hypotension
- Difficulty diagnosing epidural hematoma

Opioids

- Respiratory depression (equal to or less than with systemic opioids)
- Reduced gastrointestinal motility (greater than with systemic opioids)
- Nausea and vomiting (equal to that with systemic opioids)
- Difficult micturition (greater than with systemic opioids)
- Pruritus (much greater than with systemic opioids)

CLINICAL CONNECTION

The US Food and Drug Administration (FDA) set the safe 24-hour dose limit of acetaminophen at 4000 mg for adults. No combination analgesic prescription contains more than 325 mg of acetaminophen per unit dose.

Chronic Pain Syndromes

Surgery or trauma causing acute pain can lead to central sensitization and persistence of pain after the peripheral lesion has resolved. It is unknown how frequently this problem leads to chronic pain syndrome, but data that are accumulating suggest that specific treatment in the acute period may reduce the likelihood of a neuropathic problem later.

Neuropathic pain may start with nerve injury, which results in axon degeneration and regeneration. In animal models, abnormal discharges at the spinal cord level are associated with this process, leading to sensitization, abnormal sensation, phantom pain, and rapid changes in the functional architecture of the pain pathways at the level of the spinal cord and lower brain. *Hyperesthesia* (increased and unpleasant sensitivity to all sensory modalities), *hyperpathia* (increased unpleasant abnormal feeling from mildly uncomfortable stimuli), and *allodynia* (painful feeling from gentle stimuli) have occurred soon after acute painful trauma in some patients, especially after surgery on or near major nerve trunks. In some patients, this process may persist and advance to result in a chronic pain syndrome.

The characteristics of neuropathic pain include evidence of a primary injury; pain involving (but not confined to) a body area with a sensory deficit; a burning, electric, or shooting character of the pain; dysesthesias in the area; pain spreading beyond the cutaneous nerve distribution; sympathetic hyperactivity; and allodynia, hyperpathia, and hyperalgesia. In some complex regional pain syndromes, autonomic deregulation results in skin changes, edema, and nail and hair loss. This syndrome may lead to severe suffering and incapacitation. Once established, neuropathic pain is poorly responsive to analgesic treatment, but the pain may respond to sympathetic interruption or α -receptor blockade.³⁰ Modification of the initial pain input possibly may decrease the incidence or reduce the severity of the syndrome that develops over time.

Preemptive analgesia is the delivery of adequate and appropriate analgesia before initiation of nociceptive input from the surgical incision. By totally abolishing the painful stimulus, the potential for chronic pain syndromes should be reduced. Although general anesthetics and opioids do modify the central sensitization

TABLE 20.11 Examples of Combinations of Nonsteroidal Antiinflammatory Drugs and Opioid Analgesics

NSAID		OPIOID		
Agent	Dose (mg)	Agent	Dose (mg)	Brand Name
Acetaminophen	325	Hydrocodone	5	Anexsia 5/325
Aspirin	325	Oxycodone	4.8335	Percodan
Acetaminophen	325	Oxycodone	5	Percocet
Acetaminophen	300	Codeine	15	Tylenol No. 2
Acetaminophen	300	Codeine	30	Tylenol No. 3
Acetaminophen	300	Codeine	60	Tylenol No. 4
Ibuprofen	200	Hydrocodone	7.5	Generic

to some extent, regional analgesia, antiinflammatory agents, central α -receptor blockers, and *N*-methyl-D-(+)-aspartate (NMDA) receptor antagonists, used alone or in combination, offer hope of preempting pain and eliminating postoperative pain syndromes.

Anesthesia

The state of general anesthesia is a drug-induced absence of perception. Stronger stimuli may require deeper anesthesia. Anesthetics are usually administered by inhalation or intravenously because of the more predictable time course of drug actions. Often combinations of drugs are used to achieve the state of anesthesia. The ideal anesthetic would include the following:

- Pleasant experience with rapid induction and emergence
- Rapid changes of depth of anesthesia to match surgical demands
- Skeletal muscle relaxation to facilitate surgical exposure
- A wide margin of safety
- No toxic or adverse effects

The first and most common anesthetic agents are gases and volatile liquids (Table 20.12). Dosage and potency are compared by using the concept of minimal alveolar concentration (MAC), which is the amount necessary to achieve the anesthetic state. This is a statistical concept, similar to the ED_{50} (effective dose for 50% of subjects to respond), based on the measured agent concentration in exhaled gas (which is in equilibration with the blood) sufficient to prevent movement on surgical incision in half of the subjects. The mechanisms by which anesthetic gases and vapors exert their effects are poorly understood but may be receptor mediated (the GABA receptor being a top candidate) or may be a more diffuse, temporary disruption of nerve cell communication. The facts that anesthetic vapor potency is linearly related to fat solubility and that anesthetics can be reversed by high pressures (50–100 atmospheres) suggest that cell wall swelling from the agent dissolving in the lipid membrane is an important contributor to the anesthetic state.

Volatile anesthetics by themselves achieve some of the characteristics of the ideal anesthetic in that depth of anesthesia can be changed rapidly, induction and emergence are rapid (with some agents), and there are few toxic concerns. These agents do not reliably provide muscle relaxation. Neuromuscular blockers and other adjuvant drugs are often titrated to create the desired anesthetic state and to prevent potent agent overdose. Neuromuscular blockers are discussed in Chapter 18. Their use in anesthesia includes facilitation of tracheal intubation (often a short-acting agent) and surgical relaxation, which is necessary for intrathoracic, intraabdominal, and other procedures. Pharmacologic reversal of long-acting neuromuscular blocking agents is also discussed in Chapter 18.

Because volatile anesthetics provide little analgesia, narcotic and nonnarcotic analgesics are often a part of the anesthetic mixture. Analgesics may reduce the amount of volatile agent necessary to achieve anesthesia. Induction of general anesthesia is usually

facilitated by a rapidly effective sedative–hypnotic agent, although inhalation induction with a newer volatile agent (sevoflurane) is rapid and not unpleasant. Table 20.13 lists commonly used anesthetic induction agents.

KEY POINT

The use of a mixture of agents to achieve the anesthetic state is often referred to as *balanced anesthesia*, in which each element is provided, in balance, by a different drug.

CLINICAL CONNECTION

Administration of ketamine in the emergency room to treat acute asthma exacerbation in children is not uncommon. However, studies have not proven it to be effective in the treatment of bronchospasm.

Depth of anesthesia is determined by patient response to painful stimuli and is often judged by the sympathetic response—that is, a change in heart rate or blood pressure. Because other factors may influence these signs, determination of anesthetic depth is much more an art than a science. Monitors that are based on the processed electroencephalogram are available and are touted to predict depth of anesthesia (bispectral index [BIS] monitor), but these devices are subject to other influences as well. During the course of surgery and anesthesia, the degree of surgical stimulus and the depth of anesthesia vary, and one function of the anesthesiologist is to match these two. Analgesia may be needed intraoperatively and as a part of pain management in the postoperative period. In medically compromised patients, the main activity of the anesthesiologist is to obtain and maintain stability and prevent death; the anesthetic may simply consist of preventing pain and abolishing recall of intraoperative events. The entire cardiovascular armamentarium may be used as part of anesthetic management for these critically ill, unstable patients.

Anesthetic induction agents are used in other areas of care, including the intensive care unit (ICU) and the emergency department, and in conscious sedation. Although diazepam, lorazepam, and midazolam are commonly used agents, ketamine, propofol, and fentanyl are indicated and used in the ICU and in emergency department procedures. These agents may affect patients differently, so close monitoring is indicated. Monitoring of ventilation and cardiac function by the respiratory therapist (RT) is of utmost importance.

TABLE 20.12 Gases and Volatile Liquids Used to Produce General Anesthesia

Class	Agent	Common or Brand Name
Gases	Nitrous oxide	Laughing gas
Liquids	Isoflurane	Forane
	Sevoflurane	Sojourn, Ultane
	Desflurane	Suprane

TABLE 20.13 Anesthetic Induction Agents

Class	Generic Drug	Brand Name
Barbiturates	Methohexital	Brevital
Benzodiazepines	Diazepam	Valium, Valtoco, Diastat, Diastat Acudial
	Lorazepam	Ativan, Loreev XR
	Midazolam	Nayzilam, Seizalam
Miscellaneous agents	Etomidate	Amidate
	Ketamine	Ketalar, Spravato
	Propofol	Diprivan

XR: extended release.

Conscious Sedation

KEY POINT

Conscious sedation is a technique that uses sedatives and analgesics to prevent patient discomfort during invasive procedures. To prevent a catastrophe, a dedicated individual must monitor the progress of sedation and be prepared to correct airway and cardiovascular problems.

KEY POINT

The pain experience, including the physical and emotional components, associated with clinical interventions is unnecessary and may increase the risk of morbidity and mortality. For these reasons, minimizing fear and pain is an important part of clinical care.

Fear and pain are frequent side effects of many clinical interventions. Besides general anesthesia, many approaches are available to modify the unpleasant experience of diagnostic and therapeutic procedures. Patient preparation, education, relaxation exercises, hypnosis, and drugs may be useful. **Conscious sedation** is the term applied to pharmacologic modification of painful and frightening experiences during medical procedures. As implied by this term, sedated patients should remain conscious and able to communicate, protect their own airway, and breathe adequately. Improved patient comfort and outcome are the goals of sedation. However, because of variations in patient responses, consciousness and the patient's ability to maintain an unobstructed airway may be lost during sedation.

Institutional standards for safe and effective provision of conscious sedation are required by the Joint Commission on Accreditation of Healthcare Organizations and other regulatory agencies. These standards must be adhered to throughout the institution, whether sedation is provided by a nurse, RT, anesthesiologist, or other health care provider. Many concerned groups have developed guidelines for providing safe conscious sedation. RTs should

understand sedative and analgesic pharmacology and may actively participate in provision of conscious sedation.^{31–33} Because most of the serious complications of conscious sedation relate to airway compromise, RTs are uniquely qualified to safeguard patients and improve outcomes during conscious sedation.

Standards for Providing Conscious Sedation

Most guidelines for conscious sedation and many clinical reports differentiate several levels of sedation. Often a clear distinction is drawn between conscious sedation and deep sedation.³⁴ However, the progression from conscious sedation to deep sedation to general anesthesia is difficult to control clinically, and each deeper level implies increased risks and mandates more intensive monitoring and an increased level of support. The definitions of these states and suggested requirements for monitoring are given in **Table 20.14**.

All published conscious sedation standards insist on the presence of *more than one* person during the period of sedation (at least the operator and a monitoring assistant). Several guidelines suggest that deep sedation and general anesthesia are *indistinguishable* and that at least three qualified people must be continually present during the sedation period.³⁵ The standards also suggest that one person must have, *as sole responsibility*, continual monitoring of the patient and recording of vital signs. When providing conscious sedation, it is necessary to assess continuously and ensure oxygenation, ventilation, and temperature maintenance.

Although some conscious sedation guidelines suggest ways to monitor these vital functions, the decision to use a particular device and frequency of repeated observations is left to the clinician who is responsible for making it.³⁶ What is not left to the discretion of the clinician is the number of personnel necessary and determining that they are specially qualified and assigned *only* to monitor one patient's vital functions and the progress of sedation. Resuscitation equipment must be immediately available, as well as

TABLE 20.14 Levels of Sedation and Recommendations for Monitoring

Level of Sedation	Definition	Suggested Monitors
Conscious sedation	Minimally depressed level of consciousness, retaining patient's ability to maintain airway independently and continuously and to respond to physical stimulation and verbal commands	Dedicated monitoring assistant ECG monitoring Pulse oximetry IV access Blood pressure measurement every 15 minutes
Deep sedation	Depressed consciousness accompanied by partial loss of protective reflexes and inability to respond purposefully to verbal command	Skilled airway person Monitoring and recording person IV access Pulse oximetry Continuous ECG monitoring Blood pressure measurement every 5 minutes
General anesthesia	Unconsciousness accompanied by partial or complete loss of protective reflexes and inability to maintain airway independently	Anesthesia personnel Anesthesia assistant IV access Pulse oximetry Carbon dioxide measurement device Continuous ECG monitoring Blood pressure measurement every 5 minutes Other requirements dictated by patient's physiologic condition

ECG, Electroencephalography; IV, intravenous.

TABLE 20.15 Central and Peripheral Nervous System–Stimulating Drugs

Class	Use	Generic Drug	Brand Name
Sympathomimetics	Diet	Benzphetamine	Generic
		Diethylpropion	Generic
		Phendimetrazine	Bontril PDM
		Phentermine	Adipex-P, Lomaira, Qsymia
	Diet and CNS stimulant	Amphetamine	Adderall
	Diet and CNS stimulant	Methamphetamine	Desoxyn
	CNS stimulant	Dextroamphetamine	Dexedrine
Xanthines	CNS stimulant	Caffeine Citrate	Generic
Progestational agent	CNS stimulant	Medroxyprogesterone acetate	Provera
Respiratory stimulant	Peripheral chemoreceptor stimulant	Doxapram	Dopram
Miscellaneous	ADHD	Dexmethylphenidate	Azstarys, Focalin, Focalin XR
		Methylphenidate	Adhansia XR, Aptensio XR, Azstarys, Daytrana, Jornay PN, Methylin, Quillivant XR, Ritalin, Methylin, Concerta

ADHD, Attention-deficit hyperactivity disorder; CNS, central nervous system, XR, extended release.

individuals trained to use it. Competency in providing conscious sedation requires didactic understanding of the pharmacology of the drugs discussed in this chapter and performance-based competency, including intravenous therapy, monitor use, and supervised clinical practice.³⁷

Central Nervous System and Respiratory Stimulants

KEY POINT

CNS-stimulating drugs include methylxanthines (caffeine and aminophylline) and doxapram. These agents have little clinical usefulness in treating respiratory failure or drug-induced respiratory depression.

CLINICAL CONNECTION

Specific antagonists for benzodiazepine sedative drugs and opioids are more useful for reversing drug-induced hypoventilation.

In contrast to most of the sedative drugs discussed in this chapter, some drugs can *increase* the activity of the brain, rather than depressing it. Such drugs are termed *analeptic* drugs. If the effects are primarily on the respiratory center, the agent may be a respiratory or ventilatory **stimulant**. Stimulant drugs are used for treatment of narcolepsy, attention-deficit hyperactivity disorder (ADHD), obesity, and, to a lesser extent, respiratory failure. Some of these drugs are listed in Table 20.15. Most stimulant drugs are sympathomimetics, acting directly on α and β receptors. Their abuse potential is great, and their side effects are predictable. They interfere with sleep and are used (and abused) to promote wakefulness and weight loss.

Some drugs can increase ventilation. Doxapram was used in the past as a treatment for acute and chronic respiratory failure. It was given intravenously and caused a transient increase in the

rate and depth of ventilation. Doxapram is rarely used at the present time because no sustained improvement of respiratory failure has been demonstrated. Methylxanthines, used to promote bronchodilation, also increase catecholamines and increase ventilation. Caffeine, a common component in popular beverages, is used therapeutically in apnea–bradycardia syndromes of premature birth. Some agents that cause metabolic acidosis, such as salicylates, including carbonic anhydrase inhibitor diuretics, can increase ventilation in response to the systemic acidosis that develops. However, this increase in minute ventilation is not considered therapeutic. Progesterone can cause a sustained increase in ventilation and decrease in PaCO_2 and is occasionally used to treat chronic elevations in CO_2 from advanced obstructive lung disease. Hormonal effects on mood and breast development limit its usefulness.

Respiratory failure resulting from sedative or opioid drug overdose should be treated with specific antagonists flumazenil and naloxone rather than with nonspecific analeptic drugs. Respiratory stimulants have little or no clinical role in treating respiratory failure. Elevated PaCO_2 caused by muscle fatigue from increased work of breathing as a result of chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), or severe bronchospasm would not be expected to improve with catecholamine-stimulating agents. Mechanical ventilation, muscle rest, and bronchodilators are more appropriate approaches.

SELF-ASSESSMENT QUESTIONS

Answers can be found in Appendix A.

1. What is the difference between sedation and analgesia?
2. Identify the general class (sedative–hypnotic, analgesic, tranquilizer, anesthetic, antipsychotic) of each of the following agents: lorazepam, phenobarbital, doxapram, chloral hydrate, thiopental, midazolam, nitrous oxide, chlorpromazine, halothane, morphine, ibuprofen.
3. You are planning to extubate and remove a patient from the ventilator. However, the nurse administers a large dose of lorazepam (Ativan) for anxiety. What problem may occur if you proceed?

4. What is the most serious side effect of tranquilizers, sedatives, or analgesics (especially opioids)?
5. You have two patients, both of whom have overdosed on CNS depressants: *Patient 1 is comatose, cyanotic, with dilated pupils. Patient 2 is comatose, cyanotic, with pinpoint pupils.* Which patient may have taken a barbiturate and which may have taken a narcotic analgesic?
6. Identify your initial priorities as a respiratory therapist in caring for a patient with an overdose of tranquilizers.
7. What is the mode of action of the benzodiazepines?
8. Identify an agent that can reverse the effects of benzodiazepines, such as midazolam and triazolam.
9. Would barbiturates be helpful in managing pain in a ventilated patient?
10. Would meperidine be helpful in preventing or lessening the perception of pain?
11. Suggest an analgesic for minor pain for a patient with a bleeding disorder, such as hemophilia, or a patient who is taking an anticoagulant, such as warfarin.
12. Are there any serious side effects to the use of a ventilatory stimulant, such as doxapram?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 35-year-old Black man was admitted to the hospital with lethargy after being found in his apartment by a friend. An empty bottle of amitriptyline pills was lying next to the man. In the emergency department, the patient became more lethargic to the point of unresponsiveness and developed hypopnea and bradypnea. He was subsequently intubated and mechanically ventilated with a volume-cycled ventilator. The patient had a history of depression but had been in good physical health. He was taking amitriptyline, which was prescribed by his psychiatrist for his depression. In an act of despair, he had taken an overdose of his medication. The man had no allergies, and his past medical history and family history were unremarkable.

Physical examination revealed a mesomorphic man appearing his stated age, markedly sedated, intubated, and mechanically ventilated. His vital signs were as follows: rectal temperature (T) 39°C, pulse (P) 140 beats/min, respiratory rate (RR) 12 breaths/min on an assist/control (A/C), and blood pressure (BP) 110/60 mm Hg taken in right arm in the supine position. Head, eyes, ears, nose, and throat (HEENT) were unremarkable except for the oral endotracheal tube (ETT) in place. His chest had normal resonance to percussion, and his lungs had clear breath sounds bilaterally. Cardiovascular examination revealed, on palpation, that the point of maximal impulse was located normally in the fifth intercostal space in the midclavicular line. Auscultation revealed normal S₁ and S₂ without murmurs, gallops, or rubs. He had normal jugular venous pressure, and his pulses were 2+ throughout. His abdomen was mildly distended, with absent bowel sounds. No masses or organomegaly were present. His extremities were unremarkable, and his skin was very warm and dry. He was unresponsive to visual, auditory, or tactile stimuli, and his pupils were equally dilated and sluggishly responsive to light. All extremities were flaccid, and his reflexes were 1+ throughout. His plantar reflexes were downgoing.

Laboratory results were normal for hemography, electrolytes, blood urea nitrogen (BUN), creatinine, and liver function. The tricyclic antidepressant (TCA) level was in the toxic range. His chest radiograph was normal. The ETT was approximately 2 cm above the carina. The electrocardiogram showed sinus tachycardia at 140 beats/min, with prolonged P-R and QRS intervals. Arterial blood gas (ABG) results on A/C ventilation at 12 breaths/min, with a tidal volume (V_t) of 800 mL and a fraction of inspired oxygen (F_iO₂) of 1, were as follows: pH of 7.44, partial pressure of arterial carbon dioxide (PaCO₂) of 38 mm Hg, and partial pressure of arterial oxygen (PaO₂) of 550 mm Hg.

TCA overdose was diagnosed, and the patient was admitted to the medical intensive care unit (MICU), where he was treated with activated

charcoal 30 g via nasogastric tube q6h, along with normal saline hydration intravenously. After the first dose of charcoal, his heart rate dropped to approximately 120 beats/min, and F_iO₂ was eventually tapered to 0.35, with the resulting ABG values: pH 7.43, PaCO₂ 40 mm Hg, and PaO₂ 175 mm Hg. Several hours after the second charcoal dose, the patient awoke and was able to write notes to the MICU staff, stating that he was anxious to be extubated. The staff obliged and placed him on a T-piece with 35% oxygen (O₂) from a large-reservoir nebulizer. About 2 hours later, the patient fell asleep while on the T-piece, and ABG results at that time were pH 7.36, PaCO₂ 48 mm Hg, and PaO₂ 165 mm Hg. An astute respiratory therapist (RT) noticed the marked change in the ABG parameters and placed the patient back on the ventilator. The patient was eventually able to be extubated uneventfully several hours after the fourth dose of charcoal. He was transferred in stable medical condition to the psychiatry service the day after extubation.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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21

Vasopressors, Inotropes, and Antiarrhythmic Agents

HENRY COHEN, ROMAN FAZYLOV, NICOLE CECILE DAVIS

CHAPTER OUTLINE

Overview of Cardiovascular System

Factors Affecting Blood Pressure

Agents Used in the Management of Shock

Catecholamines

Norepinephrine (Levophed) and Epinephrine (Adrenalin Chloride)

Isoproterenol (Isuprel)

Dopamine

Phenylephrine

Vasopressin (Pitressin)

Midodrine (Proamatine)

Angiotensin II – GIAPREZA

Vasopressor-Induced Extravasation and Management

Inotropic Agents

Dobutamine

Phosphodiesterase Inhibitors: Inamrinone and Milrinone

Cardiac Glycosides: Digoxin (Lanoxin)

Electrophysiology of Myocardium

Ablation With Radiofrequency Current

Implantable Cardioverter-Defibrillators

Pharmacology of Antiarrhythmics

Class IA

Quinidine

Procainamide

Disopyramide

Class IB

Lidocaine

Mexiletine

Tocainide

Class IC

Flecainide (Tambocor)

Propafenone (Rythmol)

Class II

β Blockers

Class III

Amiodarone (Cordarone)

Dronedarone (Multaq)

Dofetilide (Tikosyn)

Sotalol (Betapace and Betapace AF)

Ibutilide (Corvert)

Class IV

Calcium Channel Blockers

Miscellaneous

Digoxin (Lanoxin)

Adenosine (Adenocard)

Management and Pharmacotherapy of Advanced Cardiac Life Support

Sudden Cardiac Death

Epinephrine

Vasopressin

Atropine (AtroPen)

Sodium Bicarbonate

Magnesium Sulfate

Alternative Routes of Medication Administration

Intraosseous Route

Endotracheal Route

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to vasopressors, inotropes, and antiarrhythmic drugs
2. List the various components that make up blood pressure
3. Compare and contrast the mechanism of action of inotropes and vasopressors
4. Describe the various drug interactions that may occur with the use of vasopressors and inotropes
5. Design an algorithm for the management of hypotension
6. Manage extravasation injuries that occur with use of vasopressor therapy

7. Describe the normal conduction of the heart
8. Define nonpharmacologic methods of treating dysrhythmias
9. Compare and contrast the categories of the Vaughan Williams classification system
10. Define the mechanism of action of digoxin
11. List all the dysrhythmias associated with cardiac arrest
12. Design an algorithm that may be used in the management of ventricular fibrillation and pulseless ventricular tachycardia
13. Design an algorithm that may be used in the management of torsades de pointes
14. Describe the proper dosage technique of intravenous magnesium therapy in the management of torsades de pointes
15. List the routes of administering medications during cardiac arrest

KEY TERMS AND DEFINITIONS

Antiarrhythmics Group of cardiac medications that are classified according to mechanism of action; in some instances, they may have multiple mechanisms of action. The most common classification system of antiarrhythmics is the Vaughan Williams classification system, which is divided into four distinct categories and a miscellaneous section.

Arrhythmias/dysrhythmias Irregular (faster or slower) heartbeats; the term *arrhythmia* is used more frequently than *dysrhythmia*.

Atrioventricular (AV) node Link between atrial depolarization and ventricular depolarization. Bohr effect Presence of carbon dioxide aids in the release and delivery of oxygen from hemoglobin.

Cardiac output (CO) Amount of blood that is pumped out of the heart per unit of time.

Catecholamines Endogenous products that are secreted into the bloodstream and travel to nerve endings to stimulate an excitatory response.

Chronotropic Agent affecting the rate of contraction of the heart.

Diastolic blood pressure (DBP) Lowest pressure reached before ventricular ejection.

Dromotropic An agent that influences the conduction of electrical impulses. A positive dromotropic agent enhances the conduction of electrical impulses to the heart.

Inotropic Agent affecting the strength of muscular contraction.

Mean arterial pressure (MAP) Pressure that drives blood into the tissues averaged over the entire cardiac cycle.

Phosphodiesterase Enzyme responsible for the breakdown of cyclic adenosine 3',5'-monophosphate (cAMP).

Sudden cardiac death (SCD) Episode of ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, or asystole leading to loss of life.

Systolic blood pressure (SBP) Peak pressure reached during ventricular ejection.

Tachycardia Overly rapid heartbeat, usually defined as greater than 100 beats/min in adults.

Vasodilator Agent causing dilation of blood vessels.

Vasopressors Agents causing contraction of capillaries and arteries.

Ventricular fibrillation (VF) Cardiac condition in which normal ventricular contractions are replaced by coarse or fine, rapid movements of the ventricular muscle.

Overview of Cardiovascular System

The cardiovascular system regulates blood flow to the various regions of the body. Blood flow generally travels via a pressure gradient, shifting from areas of higher pressure to lower pressure. The central nervous system (CNS) relays electrical impulses through sensory receptors found systemically within the vasculature, affecting vascular tone and causing shunting of blood to and from various organ systems within the body. Vascular tone is regulated via the

sympathetic nervous system and the circulation of neurotransmitters and hormones, such as epinephrine, vasopressin, and angiotensin. Several factors exert an effect on vascular tone as a response to tissue perfusion and circulatory volume. Hypotension is commonly present in patients with autonomic dysfunction and shock. *Shock* is a life-threatening medical emergency characterized by organ hypoperfusion leading to decreased delivery of oxygen (O₂) and nutrients to tissues throughout the body. There are six types of shock; their effects on hemodynamic parameters can be seen in [Table 21.1](#).

TABLE 21.1 Hemodynamic Changes in Various Shock States

Hemodynamic Parameter	Hypovolemic/ Hemorrhagic	Neurogenic	Cardiogenic	Septic/Distributive
HR	↑	↔	↔/↑	↑
MAP	↓	↑/↓	↑	↓
CVP (5–12 mm Hg)	↓	↓	↑	↓
PCWP (10–12 mm Hg)	↓	↓	↑	↓
CO (5–7 L/min)	↓	↔/↓	↓	↑
SVR (80–1440 dyn•sec•cm ⁻⁵)	↑	↓	↑	↓

CO, Cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Factors Affecting Blood Pressure

KEY POINT

Blood pressure is dependent on cardiac function, vascular tone, and vascular volume.

Typical measurement of blood pressure is relative to a recurring cardiac cycle of atrial and ventricular contractions and relaxations (Fig. 21.1). The cycle is divided into the systolic phase and the diastolic phase. The systolic phase is the portion in which ventricular contraction occurs, resulting in ejection of blood through the aorta. Conversely, diastole is the period of ventricular relaxation and blood filling. **Systolic blood pressure (SBP)** is the peak pressure reached during ventricular ejection, and **diastolic blood pressure (DBP)** is the lowest pressure reached right before ventricular ejection. Arterial pressure is typically recorded as SBP/DBP; for example, 120/80 mm Hg. **Mean arterial pressure (MAP)** refers to the pressure that drives blood into the tissues averaged over the entire cardiac cycle. Because the cardiac cycle is pulsatile rather than continuous and because two-thirds of the normal cardiac cycle is spent in diastole, MAP is not the arithmetic mean of the SBP and DBP. MAP is defined as the product of **cardiac output (CO)** and systemic vascular resistance (SVR), as follows:

$$[2(\text{DBP}) + \text{SBP}] / 3 \text{ or } \text{MAP} = \text{CO} \times \text{SVR}$$

SVR is used to define the resistance to flow of the vasculature that must be overcome to push blood through the peripheral

circulation. CO is the amount of blood that is ejected into the aorta and travels through the systemic circulation per unit of time. CO is dependent on the sum of all local blood flow regulations and is shown in the following equation as the product of heart rate (HR) and stroke volume (SV). SV is the amount of blood ejected from the heart during systole. Changes in any of these components may alter the effects of the others.

$$\text{CO} = \text{HR} \times \text{SV}$$

Summing up all components that affect the MAP, the following equation may better illustrate how these components relate to blood pressure:

$$\text{MAP} = \text{HR} \times \text{SV} \times \text{SVR}$$

The use of therapies such as fluids, vasopressors, and inotropes to maintain cardiovascular stability is directed toward altering each of these components, as shown in Table 21.2. The various **vasopressors** currently on the market have different affinities for the various receptors located within the body and exert different effects on the hemodynamic parameters, as shown in Table 21.3. Vasopressors and inotropes are not always the first-line therapy; on the contrary, fluids are the mainstays for improving hypotensive episodes. Vasopressors and inotropes have considerable side effects, and certain medications interact with various vasopressors and inotropes, leading to alterations in hemodynamic parameters, as shown in Table 21.4.

In addition to vascular tone, another component that may affect changes in tissue perfusion is vascular volume. Intravascular volume depletion may influence SV and affect MAP as well. This

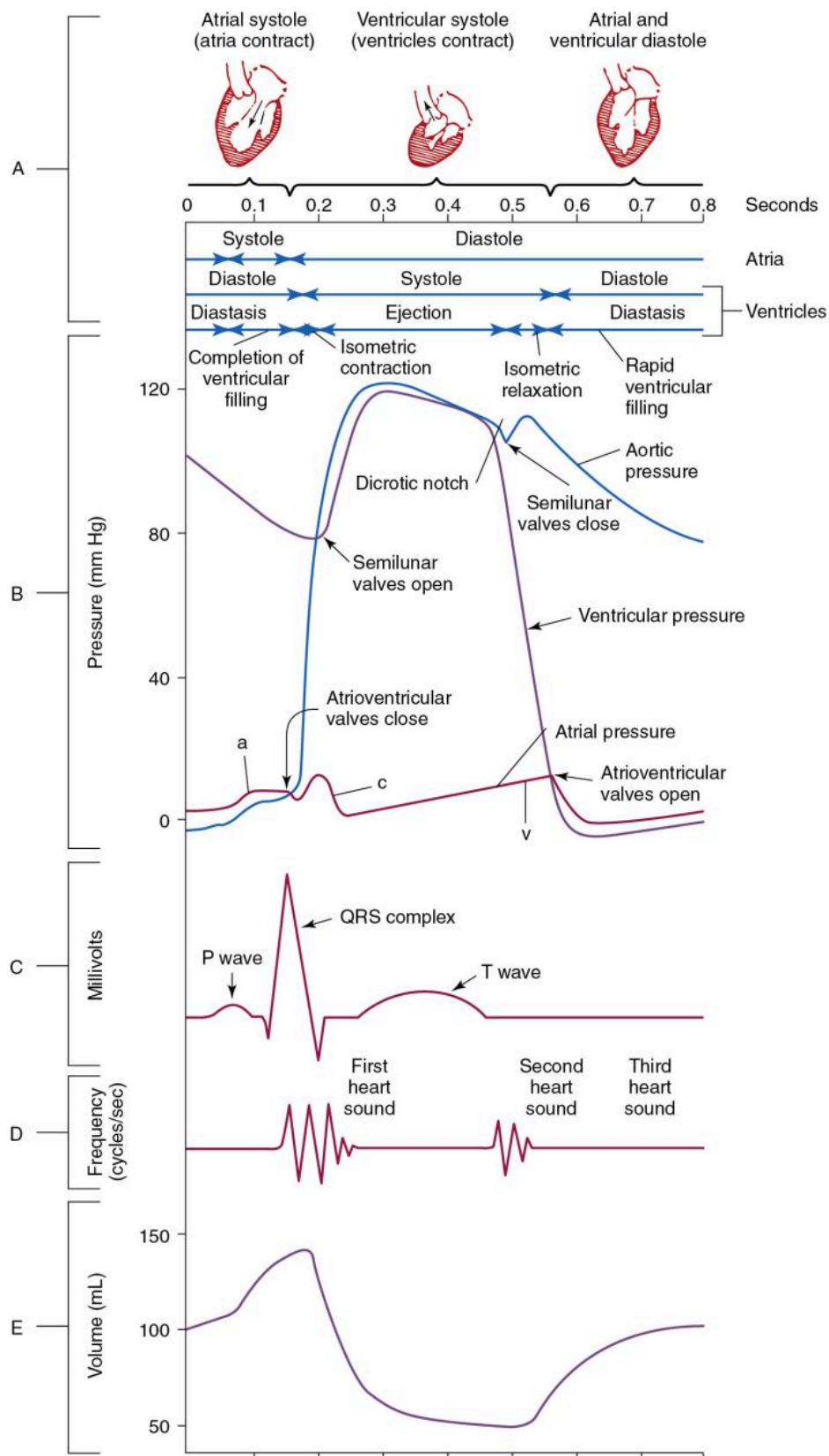
TABLE 21.2 Cardiac Drugs: Dosing, Pharmacokinetics, and Hemodynamic Effects

Agent	Dosage Range	PHARMACOKINETICS			HEMODYNAMIC EFFECTS				
		Onset (Min)	Duration	Half-Life	HR	MAP	PCWP	SVR	CO
Amrinone	0.75 mg/kg bolus, then 2.5–15 mcg/kg/min	5–10	0.5–2 hr	4.8–8.3 hr	↓	0–↓	0–↓	0–↓	↓–0–↑
Dobutamine (Dobutrex)	2–20 mcg/kg/min	1–2	10–15 min	2 min	0*	0–↓	↓	↓	↑
Dopamine (Inotropin)	1–5 mcg/kg/min	5	<10 min	2 min	0	0	0	0	0
	5–15 mcg/kg/min	5	<10 min	2 min	↑	0–↓	0–↑	↑	↑
	>15 mcg/kg/min	5	<10 min	2 min	↑	0–↓	0–↑	↑	↑
Epinephrine (Adrenalin)	0.01–0.1 mcg/kg/min	1	3–5 min	3–5 min	↑	↑	0–↓	↓†–↑*	↑
	0.1 mcg/kg/min				↑↑	↑↑	↑	↑↑	↑↑
Norepinephrine (Levophed)	0.5–30 mcg/min	1–3	5–10 min	1–2 min	0–↑	↑↑↑	↑↑	↑↑↑	0–↓
Phenylephrine (Neo-Synephrine)	0.5–5 mcg/kg/min	10–15	1–3 hr	2–3 hr	↓	↑	↑	↑	↓
Milrinone (Primacor)	50 mcg/kg bolus, then 0.375–0.75 mcg/kg/min	90	3–5 hr	2.3 hr	0–↑	↓	↓	↓	↑
Vasopressin (Pitressin)	0.01–0.04 units/min	30–60	30–60 min	10–20 min	0	↑	↑	↑	↓†
Angiotensin II (Giapreza)	20 ng/kg/min–80 ng/kg/ min	5 min	<1 min Must be given by continuous IV infusion	<1 min	0	↑	↑	↑	0

*At high doses.

†At low doses.

CO, Cardiac output; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; ↑, effect increased; ↓, effect decreased; 0, effect unchanged.



• **Fig. 21.1** The cardiac cycle. **A**, Timing of cardiac events. **B**, Simultaneous pressures created in the aorta, left ventricle, and right atrium during the cardiac cycle. **C**, Electrical activity during the cardiac cycle. **D**, Heart sounds corresponding to the cardiac cycle. **E**, Ventricular blood volume during the cardiac cycle. (From Kacmarek, R. M., Stoller, J. K., Heuer, A. J., et al. [2013]. *Egan's fundamentals of respiratory care* [10th ed.]. St. Louis, Missouri: Mosby.)

TABLE 21.3 Inotropes and Vasopressors: Receptor Affinity

Drug	α	β_1	β_2	DA
Dopamine (Inotropin)	+ to +++*	+++*	+	0/+
Dobutamine (Dobutrex)	0 to +*	0 to +*	+	0
Epinephrine (Adrenalin)	+++*	+++	++*	0
Isoproterenol (Isuprel)	0	+++	+++	0
Norepinephrine (Levophed)	+++	++	++	0
Phenylephrine (Neo-Synephrine)	+++	0	0	0

*At higher doses.

DA, Dopamine; 0, no effect; +, slight effect; ++, moderate effect; +++, pronounced effect.

component may be indirectly measured as the pulmonary capillary wedge pressure (PCWP), central venous pressure, or preload. In other words, the PCWP can be estimated by using a device called *pulmonary artery catheter* to measure the amount of fluid returning to the heart. With this measurement, the clinician can evaluate a patient-specific response to fluid therapy and vasoactive therapy. The use of a pulmonary artery catheter is associated with complications, such as infection, pneumothorax, bleeding, or thrombus formation.

KEY POINT

Cardiac drugs are used to influence cardiac function and include agents that increase myocardial contractility, regulate arrhythmias, and treat cardiac arrest.

Agents Used in the Management of Shock**CLINICAL CONNECTION**

Cardiotonic agents stimulate the myocardium and produce a positive effect. These agents include cardiac glycosides (digitalis family), β -adrenergic stimulants, dobutamine, dopamine (DA), isoproterenol, epinephrine, and phosphodiesterase inhibitors.

Catecholamines**Norepinephrine (Levophed) and Epinephrine (Adrenalin Chloride)**

Norepinephrine (Levophed) and epinephrine (Adrenalin Chloride) are endogenous **catecholamines** that are secreted by the adrenal medulla. Epinephrine is ultimately synthesized by the catalytic actions of tyrosine hydroxylase, which converts the amino acid tyrosine to levodopa and subsequently to dopamine (DA), norepinephrine, and epinephrine.^{1,2} These neurotransmitters travel to sympathetic nerve endings, where they are released to stimulate other nerve fibers and to stimulate an excitatory response. Norepinephrine and epinephrine stimulate α receptors (on the vasculature) and β receptors within the vasculature and in the myocardium. α receptors within the vasculature cause vasoconstriction, whereas β receptors cause vasodilation. Most vascular beds within the body contain β receptors; however, they are outnumbered by α receptors, so any epinephrine and norepinephrine stimulation of

β receptors is negligible or of no effect, yielding a net response of vasoconstriction. In addition, β receptors more densely populate the myocardium compared with α receptors, leading to a net effect of **tachycardia**.^{3,4}

Isoproterenol (Isuprel)

Isoproterenol (Isuprel) is a synthetic catecholamine used for the treatment of symptomatic bradycardia or torsades de pointes. Isoproterenol works solely as an agonist of β receptors. By stimulating β_1 -adrenergic receptors, it exerts pronounced **inotropic** and **chronotropic** effects. By stimulating β_2 -adrenergic receptors, isoproterenol leads to smooth muscle relaxation of the bronchi, skeletal muscle, vasculature, and gastrointestinal tract. In certain patients, this vasodilation of vascular smooth muscle may lead to hypotension, if not accompanied by another vasopressor with α activity. Venous return to the heart is also increased by vasodilation of the venous bed. The use of isoproterenol is limited because of its pronounced stimulatory effect on HR.⁴

Dopamine

DA is an endogenous catecholamine that is a precursor to norepinephrine. The usual vasopressor dose of DA is 5 to 20 mcg/kg/min; DA directly stimulates β receptors, producing chronotropic and inotropic effects and leading to increased CO, and stimulates peripheral α receptors, causing increased SVR.

Previously, low-dose DA (1 to 5 mcg/kg/min) was thought to stimulate selectively the DA₁ and DA₂ receptors in the splanchnic and renal artery beds, causing vasodilation and increased blood flow. This belief has been nullified, and use of low-dose DA is considered an obsolete form of practice. It has been suggested that improvement of renal and splanchnic blood flow as a result of DA stems from its benefits on CO, which enhances perfusion to all major organs, including blood flow to the kidney.

There is a higher likelihood of adverse effects occurring with higher doses of DA when used in patients with cardiac failure because of the increase in afterload and myocardial O₂ demand. Adverse effects include tachyarrhythmias, ectopic beat, palpitations, and decreased perfusion.

At doses that are often required for patients with septic shock (e.g., “high-dose DA”), there is an increased risk of tachyarrhythmias compared with the risk with other vasopressors. This is an artifact of the higher affinity of DA for β_1 receptors. Consequently, the updated 2021 Surviving Sepsis Guidelines⁵ recommend the use of DA be limited to highly selected patients (i.e., those with myocardial dysfunction). Overall, norepinephrine is considered a more potent vasopressor than DA and is given a strong recommendation as an initial therapy over DA in the setting of septic shock.⁵

Phenylephrine

In contrast to epinephrine, phenylephrine is purely an α agonist, yet it differs from epinephrine only in that it lacks a hydroxyl group (–OH) on the benzene ring. Phenylephrine induces vasoconstriction in most vascular beds, elevating SBP and DBP. Phenylephrine exerts an effect on systemic blood pressure by elevating total peripheral resistance.

Because of the unopposed α_1 stimulation in the vasculature causing increased SVR, patients on phenylephrine infusions develop a reflex bradycardia. This effect may be useful in patients who develop tachyarrhythmia while receiving norepinephrine infusions. In patients who develop arrhythmias, such as atrial fibrillation with rapid ventricular response (RVR), some evidence

TABLE 21.4 Drug Interactions

Precipitant Drug*	Effect	Object Drug*	Comments
<u>Dobutamine, Isoproterenol, Norepinephrine</u>			
Bretylium	↑	Dobutamine, isoproterenol, norepinephrine	Concomitant use may potentiate effects of vasopressors, causing arrhythmias
Halogenated hydrocarbon anesthetics			
Guanethidine			May increase pressor response, causing severe hypertension
Oxytocic drugs			
Tricyclic antidepressants			
<u>Phenylephrine</u>			
Bretylium	↑	Phenylephrine	Concomitant use may potentiate effects of vasopressors
Guanethidine			
Halogenated hydrocarbon anesthetics			
Oxytocic drugs			
Tricyclic antidepressants	↔		Tricyclic antidepressants may increase effects of phenylephrine
<u>Dopamine</u>			
Dopamine	↓	Guanethidine Phenytoin Dopamine	Antihypertensive effects of guanethidine may be reversed
			Concomitant use may lead to seizures, severe hypotension, and bradycardia
Tricyclic antidepressants			Tricyclic antidepressants may increase effects of dopamine
Halogenated hydrocarbon anesthetics	↑	Dopamine	May sensitize myocardium to actions of vasopressors, causing arrhythmia
MAOIs			Dopamine is metabolized by MAOIs. MAOIs increase pressor response to dopamine by 6-fold to 20-fold
Oxytocic drugs			Concomitant use may cause severe hypertension
<u>Epinephrine</u>			
Cardiac glycosides	↑	Epinephrine	May sensitize myocardium to actions of vasopressors, causing arrhythmia
Halogenated hydrocarbon anesthetics			
Levothyroxine antihistamines (chlorpheniramine, diphenhydramine)			
MAOIs			Concomitant use may cause severe hypertension
Methyldopa			
Oxytocic drugs			
Reserpine			
Sympathomimetics			
Tricyclic antidepressants			
β Blockers			
α Blockers	↓		Vasoconstricting and hypertensive effects of pressor may be reversed
Chlorpromazine		Guanethidine	Epinephrine may antagonize effects of guanethidine, resulting in decreased antihypertensive effects
Diuretics			
Epinephrine			
<u>Digoxin</u>			
Amiodarone	↑	Digoxin	Amiodarone may increase digoxin blood level; reduce digoxin dose by 50%
β Blockers			Combination may cause advanced or complete heart block
Calcium channel blockers			
Calcium			Rapid administration of intravenous calcium may result in fatal arrhythmias
Succinylcholine			Succinylcholine may cause sudden extrusion of K ⁺ from muscle cells, leading to arrhythmias
Sympathomimetics			Combination may cause increased risk of cardiac arrhythmias
Thiazide and loop diuretics			Diuretic-induced electrolyte disturbances may predispose to digitalis toxicity
Thyroid hormones	↓	Digoxin	Thyroid hormones may reduce digoxin blood levels; hypothyroid patients may require higher dose of digoxin

*Precipitant drug refers to the drug that causes the interaction; object drug refers to the drug affected by the interaction.

↑, Object drug increased; ↓, object drug decreased; ↔, object drug unaffected.

MAOIs, Monoamine oxidase inhibitors.

suggests a switch from norepinephrine infusions to phenylephrine infusions may be more likely to achieve a faster time to rate control.⁶ Initial phenylephrine infusions are usually started at 5 mcg/kg/min (or alternatively 100–180 mcg/min) and similarly to other vasopressors, rates can be titrated higher as needed to maintain the targeted blood pressure.⁷

Vasopressin (Pitressin)

Besides the pressor effects of vasopressin (which are discussed subsequently in the section on advanced cardiac life support), vasopressin may be used in the setting of septic shock, not only because of its pressor effect but also because of its water-retentive effects. Vasopressin is a naturally occurring hormone, also known as *antidiuretic hormone*. Vasopressin shows affinity for V_1 and V_2 (vasopressin-1 and vasopressin-2) receptors located in the collecting ducts in the kidneys, which contribute to water conservation and concentration of urine. Vasopressin also shows affinity for the V_3 receptor located in the pituitary, leading to various central nervous system effects.⁸ The use of exogenous vasopressin was initially hypothesized to be beneficial in sepsis based on a small study finding in 19 septic patients that initially had elevated levels of vasopressin that then decreased to normal levels as shock progressed, as compared to patients experiencing cardiogenic shock in which the stress hormone remained elevated.⁹

The dose of vasopressin in septic shock is generally 0.01 to 0.04 units/min. The VASST trial utilized a dose up to 0.03 units/min (1.8 units/hour).¹⁰ Although higher doses of vasopressin may be used, the Surviving Sepsis Guidelines recommend avoiding use of higher vasopressin doses because of its propensity to cause adverse cardiovascular events, such as myocardial ischemia. Higher doses of vasopressin should be limited to refractory septic shock when adequate MAP is unable to be achieved with other vasopressors.⁵ Doses of up to 0.8 units/min have been employed for patients with variceal hemorrhage, but it is often combined with nitroglycerin infusion to limit the development of myocardial ischemia. Vasopressin can be titrated down by 0.01 units/min increments when therapy is no longer required for maintenance of MAP. Additionally, vasopressin can be turned off without a titration safely. This should be done when the overall pressor requirements are decreasing and the shock appears to be resolving. The norepinephrine requirements may increase slightly to compensate for the loss of vasopressin and this is to be expected.

Vasopressin should not be utilized as a sole agent for management of hypotension in the setting of septic shock.⁵ Precaution stems from data that indicate that vasopressin infusion may decrease splanchnic blood flow in addition to significant rates of digital ischemia. In the 2021 Surviving Sepsis Guidelines, vasopressin is recommended as an add-on agent after norepinephrine and is given a weak recommendation with a moderate quality of evidence.⁵ When given in combination with norepinephrine in the VASST trial, vasopressin has demonstrated a catecholamine-sparing effect, though the clinical significance of this is unknown.¹⁰ This is the largest vasopressin in sepsis study to date and did not show a significant difference in 28-day or 90-day mortality. In less severe states of shock (defined as requiring norepinephrine <15 mcg/min), there was a significant difference in 28-day mortality favoring vasopressin, but that difference became nonsignificant at 90 days. More severe states had no difference in mortality and rates of adverse events were not different between groups. When compared directly to norepinephrine in the VAN-ISH trial (the VAsopressin vs Norepinephrine as Initial therapy in

Septic sHock) that randomized patients in a 2×2 factorial design aiming to also assess hydrocortisone, no significant differences were found in 28-day mortality in addition to kidney injury.¹¹ One significant finding was that vasopressin reduced the risk of renal replacement therapy, though this effect was carried by primarily nonsurvivors.

Other settings in which vasopressin may be used include diabetes insipidus at doses of 5 to 10 units given intramuscularly or subcutaneously and repeated two or three times per day or given as a continuous infusion titrated to urine output.¹² In cardiac surgery, vasopressin has a role in the management of postoperative vasoplegia.¹³ In the VANCS trial, patients post cardiac surgery were randomized to vasopressin (0.01–0.06 units/min) versus norepinephrine (10–60 mcg/min) to maintain arterial pressure. The primary endpoint was a composite endpoint consisting of mortality or severe complications including stroke, mechanical ventilation >48 hours, deep sternal wound infection, reoperation, or acute renal failure with 30 days. Vasopressin demonstrated the primary outcome significantly less frequently than the norepinephrine group, primarily driven by rates of less acute renal failure. Other significant outcomes included less atrial fibrillation and shorter lengths of ICU stay and lengths of hospital stay. Vasopressin may be used to treat variceal bleeding (i.e., 0.2–0.4 units/min). Caution is needed when treating conditions other than shock with vasopressin; myocardial ischemia may ensue as a result of the potent vasoconstrictive properties at higher doses.¹⁴

Although vasopressin was developed in 1928, in 2014 it was rebranded to Vasostrict and received US Food and Drug Administration (FDA) approval for use in septic shock. This led to its cost being driven up several thousand percent in the United States, which promoted a closer look into its role in septic shock. However, at the end of 2021, the FDA approved a vasopressin generic option, hopefully leading to more appropriate costs.

Midodrine (Proamatine)

Midodrine hydrochloride is an oral inactive prodrug that converts to the active species, desglymidodrine, via deglycination. Desglymidodrine is an α_1 agonist. Midodrine is indicated for the management of orthostatic hypotension. However, because midodrine can cause significant hypertension and reflex bradycardia, it should only be used in patients with orthostatic hypotension that is refractory to treatment and severe enough to impair daily living—this is also noted as an FDA boxed warning (so called for the box surrounding the warning located in the manufacturer information sheet or the package insert) in the product labeling.¹⁵ Midodrine has an off-label indication in hepatorenal syndrome (HRS) (5–15 mg 3 times daily) as an alternative to terlipressin to be used in combination with albumin and octreotide. Data supporting this practice are poor with small populations and are retrospective in nature but appear to indicate improvement in mean arterial pressure, mortality, and resolution of HRS.^{16,17}

Although not labeled for use in shock, midodrine has been used to wean patients from intravenous (IV) vasopressors and transition them from the intensive care unit to general medical floors.¹⁸ This practice was evaluated in the 2020 MIDAS trial, which randomized patients with hypotension unable to be liberated from vasopressors to midodrine 20 mg every 8 hours versus placebo.¹⁹ While the results did not demonstrate significant differences in time to vasopressor discontinuation or other secondary endpoints, other retrospective studies indicate promising results. The MIDAS trial had difficulties enrolling patients, requiring 7 years to enroll

136 participants with generous enrollment criteria, and baseline MAPs were in the 70s, which is higher than the conventional MAP target of 65 mmHg in most septic patients. While it has a favorable side effect profile, midodrine is associated with rates of bradycardia, which is supported by findings in the MIDAS trial. Additionally, another limitation from the MIDAS trial may be the frequency at which midodrine was administered. Recent evidence indicates administering midodrine every 6 hours could be beneficial, which is supported by the peak effect of desglymidodrine in 1 to 2 hours and short half-life of 3 to 4 hours.²⁰

Angiotensin II – GIAPREZA

Angiotensin II is the most recently approved vasoconstrictor approved to increase blood pressure in adult patients with septic or other distributive shock. Angiotensin II is an endogenous catecholamine that increases blood pressure as well as increase fluid retention secondary to increased aldosterone release. Direct action of angiotensin II on the smooth muscle is mediated by binding to the G-protein–coupled angiotensin II receptor on smooth muscle cells, which stimulates ionized calcium (Ca^{2+})/calmodulin phosphorylation of myosin and causes smooth muscle contraction. The recommended starting dose is 20 ng/kg/min via a continuous infusion and is titrated to goal blood pressure. Central line is preferred to minimize the risk of extravasation. In ATHOS-3 study, patients on average reached their goal blood pressures in approximately 5 minutes and angiotensin II in combination with high dose vasopressors was demonstrated to be more effective at achieving a MAP of 75 than placebo (saline) with high-dose vasopressors.²¹ After the initial 2.5 hours of study drug infusion, MAP targets were changed to 65 to 70 and the differences between angiotensin II and placebo became less clinically significant. Adverse events were not statistically significant between groups, although the FDA package insert mentions a thrombosis rate of 13%, which is higher than the rates seen in the trial. One interesting point in this trial is patients that had concomitant acute respiratory distress syndrome (ARDS) were more sensitive as a result of the relative angiotensin II insufficiency secondary to angiotensin-converting enzyme (ACE) being a pulmonary capillary endothelial-bound enzyme and being 2.03 times more likely to achieve MAP goal with concomitant ARDS.

Vasopressor-Induced Extravasation and Management

Extravasation is a well-known iatrogenic manifestation of inappropriately infused vasopressor therapy, eventually leading to necrosis and gangrene. Initial signs and symptoms of extravasation include pain, swelling, erythema, blistering, blanching, and/or mottling of the skin. As a general rule, the risk of vasopressor extravasation increases with more concentrated IV solutions. While extravasation is a risk with vasopressors, the risk is likely overstated from older data.²² More recent data indicate peripheral administration of vasopressors may be done safely and is appropriate in a variety of patients. Some strategies to mitigate risk include using a large vein in the forearm or upper arm, using a 20-gauge catheter or larger, avoiding long durations of infusions, and implementing frequent infusion site monitoring to assess for redness or infiltration. Additionally, it is prudent to avoid peripheral administration of vasopressin or angiotensin II as available extravasation literature is both lacking and indicates poor treatment options.

If appropriate monitoring is in place, most injuries from extravasation can be avoided if initial management is started early. The infusion should be stopped immediately with attempts to

aspirate as much infiltrated drug from the catheter as possible and switched to another line to maintain hemodynamic therapy. The limb should be elevated and warm compresses can be applied to promote vasodilation. Avoid cool compresses that would increase vasoconstriction.

Alpha agonists may be useful in norepinephrine extravasations. Phentolamine 5 to 10 mg diluted in 10 mL of 0.9% sodium chloride may be injected into the extravasation site multiple times with a hypodermic needle. It may also be administered through the infiltrated cannula if still in place. Phentolamine has diminished efficacy as time progresses.

Phentolamine frequently encounters drug shortages and high cost procurement, so terbutaline has been used as an alternative option for vasopressor extravasation. It is a beta-2 agonist that promotes vasodilation when injected at the site of extravasation. Terbutaline 1 mg should be diluted in 9 mL of 0.9% sodium chloride and injected subcutaneously in 1 mL increments around the area of extravasation. Topical nitroglycerin 2% ointment may also be a treatment option. Apply 1 inch to the affected area every 8 hours.

Inotropic Agents

Dobutamine

Dobutamine is indicated for the short-term treatment of decompensated heart failure secondary to depressed contractility. Dobutamine is a synthetic catecholamine that is chemically related to DA; however, in contrast to DA, it is not metabolized to norepinephrine, and it does not stimulate DA receptors.⁴ Its pharmacologic actions result from the effects of its racemic components. The (R)-isomer is responsible for its activity on the β_1 and β_2 receptors, causing predominant positive inotropic and chronotropic effects and vasodilatory effects, respectively. This combination of effects enhances CO and SV. The (S)-isomer is responsible for its activity on the α_1 receptors, causing vasoconstriction.^{1,7} The vasodilatory β_2 -adrenergic effects counterbalance the vasoconstrictive α_1 effects, leading to minor changes in SVR usually seen at lower doses. With increasing doses, the β_2 -vasodilatory actions predominate over the α_1 -vasoconstrictive effect, causing a decrease in systemic and pulmonary vascular resistance. The decline in systemic and pulmonary vascular resistance may also be secondary to enhanced CO.

As an inotropic agent, dobutamine has adverse cardiac effects, which include **arrhythmias/dysrhythmias**, increase in myocardial O_2 consumption and demand, tachycardia, and hypotension. A limiting factor when dobutamine is used for greater than 72 hours is tachyphylaxis; this may result from downregulation of β_1 receptors and may be overcome by increasing the dose. In patients with sulfite sensitivity, allergic reactions, such as anaphylaxis, or life-threatening asthmatic episodes may occur because dobutamine formulations contain sulfites.⁴

Phosphodiesterase Inhibitors: Inamrinone and Milrinone

Phosphodiesterase inhibitors (also known as *inodilators*), such as inamrinone (formerly called *amrinone*, no longer available on the US market) and milrinone, are both inotropic and vasodilator agents because they increase myocardial contractility and induce vascular smooth muscle relaxation. These effects are mitigated by inhibition of intracellular phosphodiesterase (subclass III). Phosphodiesterase is an enzyme responsible for the breakdown of cyclic adenosine 3',5'-monophosphate (cAMP). An increase in cAMP concentration mediates an increase in intracellular Ca^{2+} , which is

responsible for its inotropic effect, and cAMP-dependent protein phosphorylation, causing relaxation of vascular muscle. Hemodynamically, phosphodiesterase inhibitors cause a decrease in SVR and PCWP and an increase in CO without increasing HR or myocardial O₂ demand. These hemodynamic changes are related to plasma concentration.

Milrinone is the only intravenous phosphodiesterase inhibitor used in practice today. It has a shorter half-life than inamrinone (discontinued) and is less likely to cause thrombocytopenia. It undergoes renal elimination with an elimination half-life of 1 to 3 hours in patients with normal renal function; steady-state concentrations are reached in 4 to 6 hours if initiated without a loading dose. The risk of hypotension occurring is higher when a loading dose is given. Milrinone may be given as an initial IV bolus dose of 50 mcg/kg administered slowly over 10 minutes followed by continuous infusion at a rate of 0.375 to 0.75 mcg/kg/min and titrated to effect. Dosage adjustment should be made in patients with severe cardiac failure or renal impairment because of the considerable reduction in clearance.^{1,4,7}

Milrinone is most commonly used in heart failure with reduced ejection fraction, typically in patients who have decompensated with low cardiac output and severe left ventricular (LV) systolic dysfunction.²³ It may be used as a bridge therapy in patients who are refractory to medical management and are waiting for mechanical circulatory support or heart transplantation. Patients with LV obstruction should avoid the use of inotropes as this may cause them to worsen. Milrinone and dobutamine were compared in a randomized clinical trial in 2021 in patients with cardiogenic shock.²⁴ The composite outcome (in-hospital death from any cause, transient ischemic attack, stroke, or cardiovascular or renal events) occurred with a similar frequency in both groups (49% versus 54%) as did all secondary outcomes.

Milrinone is also used for treating and preventing delayed cerebral ischemia due to vasospasm post subarachnoid hemorrhage.²⁵ Vasospasm, which is a narrowing of the cerebral arteries, occurs 3 to 4 days after the initial bleed and can lead to areas of ischemia on the other side of the narrowed artery if not promptly treated. The cerebrovascular smooth muscle contains large amounts of phosphodiesterase III, which lends itself to vasodilation via milrinone and possibly some anti-inflammatory effects. Patients are given a bolus of 0.05 to 0.2 mg/kg when actively spasming, followed by a continuous infusion starting at 0.75 mcg/kg/min and titrated up to 1.25 mcg/kg/min. Dosing is consistently higher than seen in heart failure. This may be used in combination with vasopressors. Additionally, milrinone may be injected intra-arterially where the spasm is occurring.

Cardiac Glycosides: Digoxin (Lanoxin)

The cardiac glycoside class consists of one medication, digoxin (Lanoxin), which is used in the management of congestive heart failure (CHF). The implementation of digoxin in the treatment of CHF stems from its capacity to exert an inotropic effect on the myocardium. Cardiac glycosides reversibly inhibit the sodium-potassium-adenosine triphosphatase pump (Na⁺-K⁺-ATPase pump) located in the cardiac heart muscle, leading to a net loss of K⁺ and a net gain in intracellular Na⁺ concentration. As a result, the Na⁺-K⁺ active transport system, which pumps sodium out of the cell and calcium into the cell, is activated. Elevated Ca²⁺ concentrations result in further calcium secretion from the endoplasmic reticulum, ultimately stimulating the actin-myosin light chain reaction, resulting in myocardial contraction. Digoxin also

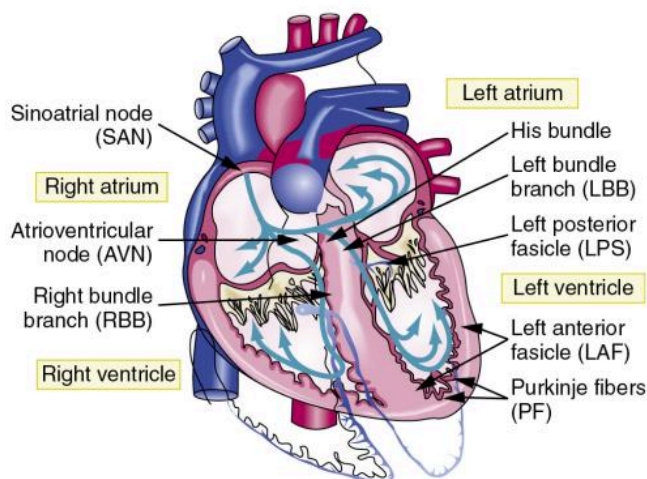
has an inhibitory effect on the vagus nerve, leading to decreased HR and **atrioventricular (AV) node** prolongation. In contrast to other inotropic agents, such as dobutamine and milrinone, digoxin generally does not exert hypotensive effects, unless directly caused by bradycardia.

Digoxin undergoes renal elimination. In the presence of renal insufficiency, accumulation of digoxin may occur. Generally, digitalis intoxication is diagnosed when mean serum digoxin concentration exceeds 2 ng/mL; however, the clinical significance of this value depends on the time of ingestion and the time of serum sampling. Digoxin has a long distribution phase. It may take 4 hours after IV administration and 6 hours after oral administration for digoxin to distribute fully out of the circulatory compartment and into other regions of the body. Serum sampling of digoxin before the distribution phase may give the impression that the serum concentration is greater than it actually is. Digoxin displays a very narrow therapeutic range (0.5–2 ng/mL), particularly in the setting of hypokalemia. Hypokalemia may potentiate the adverse effects of digoxin and render the risk of arrhythmias and death more imminent. Adequate K⁺ supplementation should be used to maintain the serum K⁺ level within the normal range.

In contrast, digitalis toxicity may cause hyperkalemia by its inhibitory actions on the Na⁺-K⁺-ATPase pump. Digoxin toxicity may manifest as serious life-threatening ventricular arrhythmias (VAs), including premature ventricular contractions, AV junctional rhythm, bigeminal rhythm, and second-degree AV blockade. Bradycardia may also occur early on in the setting of digoxin toxicity. The initial symptoms of digitalis toxicity are nausea, vomiting, anorexia, and abdominal pain. These symptoms may result from a direct effect on the gastrointestinal tract or from CNS stimulation of the chemoreceptor trigger zone. Other rare but possible neuropsychiatric effects may manifest as disorientation and hallucination, especially in older patients, and visual disturbances, such as yellow-green halos. Digoxin immune Fab is the antidote used to facilitate the speedy elimination of digoxin from the body. Digoxin immune Fab is indicated in the setting of life-threatening toxicity, such as VAs, bradyarrhythmias, ingestion of greater than 10 mg in adults or 4 mg in children, a steady-state level greater than 10 ng/mL, progressive elevation of K⁺, or a K⁺ level greater than 5 mEq/L.²⁶

Electrophysiology of Myocardium

Electrical activity is initiated by an innate pacemaker located at the sinoatrial (SA) node. Electrical potential exists across the cell membrane, and it changes in response to transmembrane movement of Na⁺, K⁺, Ca²⁺, and Cl⁻ ions. These ions mediate the process of myocardial contraction and relaxation. When an electrical stimulus is evoked from the SA node, it generates an action potential (AP). Once generated, the AP produces a local current, which evokes further APs along the myocardium. An AP elicits myocardial depolarization or contraction. The link between atrial depolarization and ventricular depolarization is a portion of the conduction system called the *AV node*. The AV node slows down the electrical impulse to ensure that atrial excitation is completed before ventricular excitation. After leaving the AV node, the impulse travels to the wall between the two ventricles via the conducting system fibers known as the *bundle of His*. From the bundle of His, the cardiac conduction system bifurcates into three main bundle branches: the right bundle and two left bundles. These bundle branches form a conduction network, referred to as



• Fig. 21.2 Cardiac conduction system.

Purkinje fibers (Fig. 21.2). The conduction system innervates the myocardium and causes changes in membrane polarization of the muscle fiber.¹⁴

An AP (Fig. 21.3) can be divided into the following five different phases:

Phase 0: Initial rapid depolarization of myocardial tissues secondary to an abrupt transmembrane influx of sodium through “fast” sodium channels

Phase 1: Fast sodium channels are inactivated; this, coupled with the movement of K^+ and Cl^- ions, leads to a transient net outward current and the beginning of repolarization

Phase 2: “Plateau” phase, maintained by a balance between calcium influx and potassium efflux

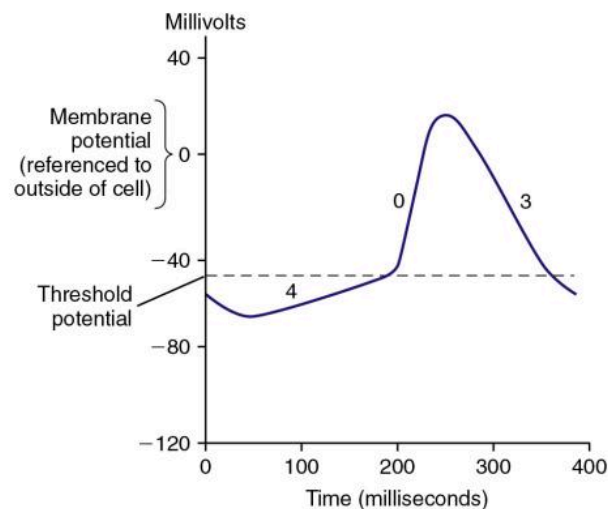
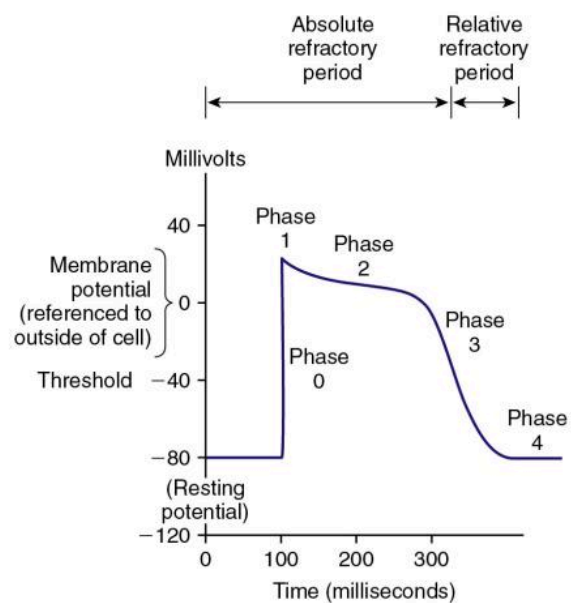
Phase 3: Calcium channels close, but membrane remains permeable to potassium, resulting in cellular repolarization

Phase 4: Cell returns to its “resting” state; the resting membrane potential is reached through gradual depolarization related to a constant sodium influx balanced by a decreasing efflux of K^+

During the AP, a second stimulus would not evoke a second AP; at this point, the membrane is said to be in the *absolute refractory period*. The absolute refractory period does not allow the heart to undergo premature contractions or to maintain a tetanic state. Arrhythmias are associated with abnormal impulse generation or conduction. Certain conditions that can precipitate arrhythmias are myocardial ischemia, CHF, oversensitivity to catecholamines, and electrolyte abnormalities.

Ablation With Radiofrequency Current

Catheter ablation is very effective when atrial fibrillation (AF) is caused by a single primary circuit. The procedure involves inserting a catheter into a blood vessel in the groin or the neck and guiding it toward the heart. When the tip of the catheter is placed against the part of the heart causing the arrhythmia, radiofrequency electrical current is applied through the catheter to produce a small burn about 6 to 8 mm in diameter. Patients should be adequately anticoagulated at least 1 month before the ablation procedure to prevent the formation of thrombi in the atria. The procedure carries a success rate in maintaining sinus rhythm over the next year of 30% to 90%.²⁷



• Fig. 21.3 Action potential diagram. (From Cairo, J. M., & Pilbeam, S P. [2010]. *Mosby's respiratory care equipment* [8th ed.]. St. Louis, Missouri: Mosby.)

Implantable Cardioverter-Defibrillators

Implantable cardioverter-defibrillators (ICDs) have been used since the 1980s to cardiovert, to terminate ventricular tachycardia (VT), and to provide backup pacing for bradycardia. ICDs are indicated for the following conditions:

- Cardiac arrest caused by pulseless VT or **ventricular fibrillation (VF)** not caused by a transient or reversible cause
- Spontaneous sustained VT
- Syncope of undetermined origin with clinically relevant, electrophysiologically inducible sustained VT or VF when drug therapy is ineffective, not tolerated, or not preferred
- Nonsustained VT in patients with coronary artery disease, before myocardial infarction, left ventricular dysfunction, and electrophysiologically inducible VT or VF not suppressed by class I antiarrhythmics

Of patients with ICDs, 40% to 70% require antiarrhythmic drug therapy, which puts them at risk for drug-ICD interactions.^{28,29}

Pharmacology of Antiarrhythmics

KEY POINT

Antiarrhythmic agents are classified into groups on the basis of their electrophysiologic action. Class I agents depress the inward sodium current and are subdivided further as IA, IB, and IC. Class II agents are β -blocking agents. Class III agents have complex effects that can prolong the action potential (AP) and in some cases exert β -blocking action. Class IV agents are calcium channel blockers. Other antiarrhythmic agents include adenosine, which is used to convert supraventricular tachycardia (SVT) into sinus rhythm.

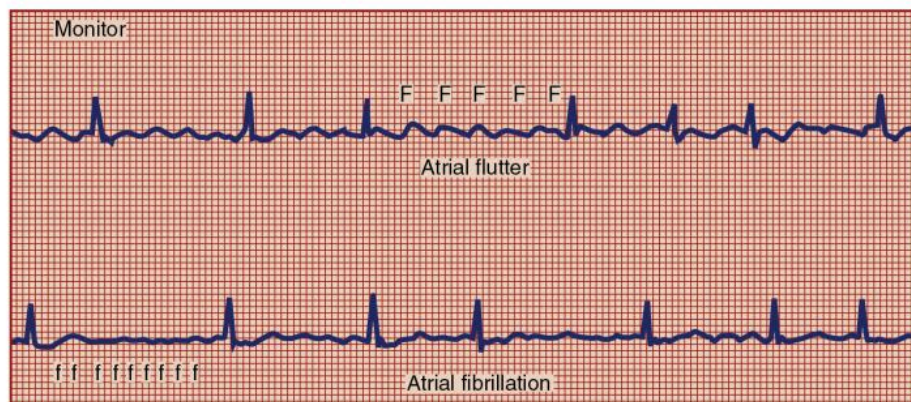
Antiarrhythmics are classified according to their mechanisms of action. In some instances, these drugs may manifest multiple mechanisms of action. The most common classification system of antiarrhythmics is the Vaughan Williams classification system, which divides antiarrhythmics into classes: I (IA, IB, IC), II, III, IV, and a miscellaneous class. Table 21.5 describes the detailed pharmacology of antiarrhythmics, and Table 21.6 lists their pharmacokinetic parameters.

Class IA

Class IA agents block fast Na^+ channels in the myocardium, specifically in the atrium. They also block repolarizing K^+ currents and may prolong the AP. As a result, class IA agents have been associated with significant proarrhythmic properties, such as Q-T interval prolongation.

Quinidine

Quinidine, although less commonly used, is efficacious in the treatment of atrial fibrillation/flutter (AF/AFL) (Fig. 21.4). The effects of quinidine on the AV node are bimodal. At lower concentrations, quinidine has antivagal properties, enhancing AV nodal conduction. At higher concentrations, the AV nodal conduction is slowed down. Because of difficulty in predicting response to quinidine, it is important to initiate a rate-controlling agent first. Quinidine should be used with caution in patients with preexisting asthma, muscle weakness, or infection with fever because hypersensitivity reactions to this medication may be masked by these conditions. Overdosage of quinidine has produced respiratory depression or distress, apnea, diarrhea, vomiting, seizures, hypotension, syncope, and electrocardiography (ECG) changes.³⁰



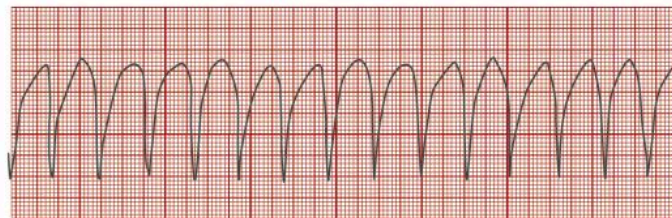
• **Fig. 21.4** Atrial flutter and fibrillation. Notice the “sawtooth” waves (F waves) with atrial flutter and the irregular fibrillatory. (From Miller, R. D., Eriksen, L. A., Wiener-Kronish, J. P., et al. [2010]. *Miller’s anesthesia* [7th ed.]. Philadelphia, Pennsylvania: Churchill Livingstone.)

Procainamide

Procainamide is available only as an IV formulation in the United States and is indicated for the treatment of VT (Fig. 21.5) that is life threatening; because of its proarrhythmic effects, including torsades de pointes (Fig. 21.6), the use of this agent for lesser arrhythmias is not recommended. In addition, procainamide has the potential to produce serious hematologic disorders, particularly leukopenia and agranulocytosis; it is used only when benefits outweigh the risks. Procainamide has also been used to convert AF/AFL to sinus rhythm. It is necessary to monitor levels of both procainamide and its active metabolite *N*-acetyl procainamide (NAPA) for efficacy and toxicity. An adverse effect unique to procainamide is the development of systemic lupus erythematosus (SLE)-like syndrome, which can manifest with pleural or abdominal pain, myalgias, arthralgias, pleural effusion, pericarditis, fever, chills, and skin lesions. SLE-like syndrome occurs in 30% of patients after prolonged administration of procainamide, especially in slow acetylators, who are at risk of accumulating the hydroxylamine metabolite responsible for the pathogenesis of this syndrome. If the lupoid syndrome does not resolve with discontinuation of procainamide, treatment with corticosteroids may be warranted.⁴

Disopyramide

Disopyramide is indicated for the treatment of life-threatening VT; it is also used for the treatment of paroxysmal supraventricular tachycardia (PSVT). Treatment with disopyramide should be initiated in the hospital. Patients with AF/AFL must receive digoxin therapy to achieve an adequate serum digoxin level before administration of disopyramide to ensure there is no further elevation of the ventricular rate. K^+ levels should be corrected before initiation of therapy because the drug may be ineffective in patients with hypokalemia, and its toxic effects may be enhanced in hyperkalemia. Disopyramide may cause or aggravate CHF or



• **Fig. 21.5** Ventricular tachycardia. (From DesJardins, T., & Burton, G. [2011]. *Clinical manifestations and assessment of respiratory care* (6th ed.). St. Louis, Missouri: Mosby.)

TABLE 21.5 Pharmacology of Antiarrhythmics

Class/MOA	Ion Block	Drug	QRS	Q-T _c	Indications	Dosages	Route
IA/↓ phase 0, ↑ AP	Sodium (intermediate)	Moricizine*	↑	0	VA	600–900 mg/day in three divided doses	PO
		Quinidine	↑	↑	AF/AFL/VA	Quinidine sulfate, 200–600 mg q 4–12 hr; quinidine gluconate, AF/AFL cardioversion and VA, 324–648 mg q 8–12 hr	PO
						Quinidine gluconate, AF/AFL cardioversion and VA, 10 mg/min infusion up to 400 mg	IV
		Procainamide	↑	↑	VA	40–50 kg, 2 g/day; 60–70 kg, 3 g/day; 80–90 kg, 4 g/day; >100 kg, 5 g/day	IV
		Disopyramide	↑	↑	VA	400–800 mg/day in divided doses, IR divided q 6 hr, CR divided q 12 hr	PO
IB/↓ phase 0 slightly; shorten AP	Sodium (fast on/off)	Lidocaine	0	0-↓	VA VT	50–100 mg (may repeat in 5 min) up to 300 mg in any 1-hr period; maintenance 1–4 mg/min 1–1.5 mg/kg; may repeat at 0.5–0.75 mg/kg q 5–10 min (maximum 3 mg/kg)	IV
		Mexiletine	0	0	VA	200–400 mg q 8 hr 150–250 mg over 10 min, then 250 mg over 30–60 min, then 250 mg over 2.5 hr, then 500 mg over 8 hr; maintenance 250–500 mg q 12 hr	PO IV
		Tocainide	0	0-↓	VA	400 mg q 8 hr, then 1200–1800 mg/day divided q 8 hr (maximum 2400 mg/day)	PO
		Phenytoin	0	↓	VA	4 mg/kg q 6 hr for 1 day, then 5–6 mg/kg/day divided q 12 hr 15 mg/kg over 1 hr (or target level of 15–20 mcg/mL)	PO IV
IC/Marked ↓ of phase 0; affect repolarization	Sodium (slow on/off)	Flecainide	↑↑	0-↑	AF/AFL/PSVT VA/VT	50 mg q 12 hr; ↑ by 100 mg q 4 days (maximum 300 mg/day) 200–400 mg/day	PO
		Propafenone	↑	0-↑	AF AFL PSVT AF/AFL/PSVT/VA	225 mg q 12 hr (SR) 325–425 mg q 12 hr (IR) 150 mg q 12 hr (IR) AF, 225 mg (SR) q 12 hr, ↑ to 325–425 mg q 12 hr; AFL/PSVT/VA, 150–300 mg (IR) q 8 hr	PO
II/↓ phase 4 (depolarization)	Calcium (indirect)	Propranolol	0	0-↓	AF/AFL/PSVT/PVC	Loading dose, 0.5–1 mg q 2 min (up to 0.1–0.15 mg/kg); maintenance dose, 0.04 mg/kg/min Maintenance dose, 10–120 mg three times daily	IV PO
		Esmolol	0	0-↓		Loading dose, 0.5 mg/kg over 1 min; maintenance dose, 50–300 mcg/kg/min (bolus between dose increases)	IV
		Acebutolol	0	0-↓		Initial, 200 mg twice a day; maintenance, 600–1200 mg/day (in two or three divided doses)	PO
		Metoprolol	0	0-↓		Initial, 2.5–5 mg q 2–5 min (up to 15 mg over 10–15 min) Maintenance dose, 25–100 mg twice a day	IV PO
		Atenolol	0	0-↓		0.5 mg/min in aliquots of 2.5 mg with 10-min interval between aliquots (maximum single dose 10 mg) Initial, 50–100 mg daily	IV PO
		Nadolol	0	0-↓		0.01–0.05 mg/kg at 1 mg/min (maximum cumulative dose 10 mg) 60–160 mg/day in single or divided doses	IV PO

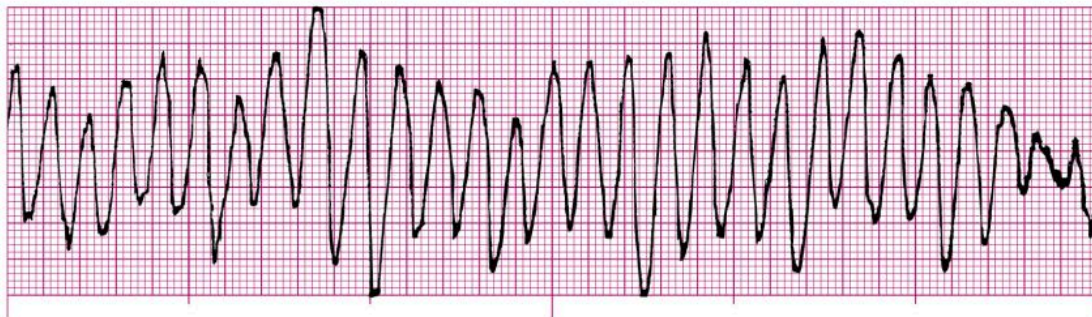
TABLE 21.5 Pharmacology of Antiarrhythmics—cont'd

Class/MOA	Ion Block	Drug	QRS	Q-T _c	Indications	Dosages	Route
III/↑ phase 3 (repolarization)	Potassium	Amiodarone	↑	↑↑	VA	800–1600 mg for 1–3 wk, then 600–800 mg for 1 mo, then 400–600 mg daily 150–300 mg bolus, then 1 mg/min for 6 hr, then 0.5 mg/min for 18 hr	PO IV
		Dronedarone	↑	↑↑	AF/AFL	400 mg twice a day with meals	PO
		Bretiylium	0	0	VA	Loading dose, 5–10 mg/kg bolus, may repeat to a maximum of 30 mg/kg, then 1–2 mg/min or 5–10 mg/kg over 8 min q 6 hr	IV
		Dofetilide			AF/AFL	Q-T _c ≤ 440 msec, 500 mcg twice a day 2–3 hr after first dose if Q-T _c increases >15% or >500 msec, ↓ dose to 250 mcg twice a day	PO
		Sotalol	0	↑↑	AF/AFL VA	CrCl >60 mL/min, 160 mg/day; CrCl 40–60 mL/min, 80 mg/day; titrate to Q-T _c <520 msec (maximum 320 mg/day) 80 mg twice a day, ↑ at 40–80 mg q 2–3 days (maximum 480–640 mg/day)	PO
		Ibutilide	0	↑↑	AF/AFL	≥60 kg, 1 mg; <60 kg, 0.1 mg/kg over 10 min (may repeat once)	IV
IV/↓ phase 4, ↑ phases 1 and 2	Calcium	Verapamil	0	0	SVT	IR, 240–320 mg/day in three or four divided doses; up to 480 mg/day in three or four divided doses for patients not on digoxin therapy 0.075–0.15 mg/kg over 2 min; may give 10 mg after 30 min if no response	PO IV
		Diltiazem	0	↓	PSVT	0.25 mg/kg over 2 min; if no response, may give 0.35 mg/kg after 15 min; maintenance, 5–10 mg/hr; ↑ in 5-mg/hr increments up to 15 mg/hr for up to 24 hr	IV
↑ phase 4 ↓ AP	Na ⁺ -K ⁺ pump	Digoxin	0	↓	SVT	8–12 mcg/kg	IV
↓ conduction time; interrupts reentry through AV node	Adenosine receptor	Adenosine	0	0	SVT	6 mg over 1–2 sec; ↑ to 12 mg q 1–2 min as needed for two doses (maximal single dose 12 mg)	IV

*Morizine does not belong to any subclass (IA, IB, or IC) of antiarrhythmic but does have some properties of each.

↑↑, high increase; ↑, increase; ↓, decrease; 0, no change.

AF, Atrial fibrillation; AFL, atrial fibrillation/flutter; AP, action potential; AV, atrioventricular; CrCl, creatinine clearance; CR, controlled release; ER, extended release; IR, immediate release; IV, intravenous; MOA, mode of action; PO, per os (orally administered); PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; QRS, QRS interval, time for ventricular depolarization; Q-T_c, Q-T interval (duration of ventricular electrical activity), corrected for heart rate; SR, sustained release; VA, ventricular arrhythmia; VT, ventricular tachycardia.



• **Fig. 21.6** Torsades de pointes arrhythmia. (From Aehlert, B. [2010]. *ECGs made easy* [4th ed.]. St. Louis, Missouri: Mosby.)

TABLE 11.6 Antiarrhythmics: Pharmacokinetics and Adverse Reactions

Drug	PHARMACOKINETICS					Adverse Reactions
	Onset (PO) (hr)	Duration (hr)	Half-Life (hr)	Therapeutic Range (mcg/mL)	Toxic Level (mcg/mL)	
Moricizine (Ethmozine)	2	10–24	1.5–3.5	NA	NA	All class I agents: Negative inotropic effect, infranodal conduction block
Quinidine (Quinaglute)	0.5	6–8	6–7	2–6	>8	Class IA: Torsades de pointes
Procainamide (Pronestyl)	0.5	≥3	2.5–4.5	4–8	>16	Quinidine: N/V/D, cinchonism (tinnitus, blurred vision, dizziness, tremor)
Disopyramide (Norpace)	0.5	6–7	4–10	40–60	>80	Procainamide: N/V/D (30%), bitter taste, rash, hepatitis, mental depression, psychosis
Lidocaine (Xylocaine)	—	0.25	1–2	1.5–6	>7	Disopyramide: Anticholinergic effects (dry mouth, blurred vision, urinary retention), hypoglycemia, cholestatic jaundice, agranulocytosis
Mexiletine (Mexitil)	—	—	10–12	0.5–2	>2	Class IB: Muscle twitch, seizures, proarrhythmia, dyspnea
Tocainide (Tonocard)	—	—	11–15	4–10	>10	Phenytoin: Hypotension, gingival hyperplasia, antiepileptic hypersensitivity syndrome
Phenytoin (Dilantin)	0.5–1	≥24	22–36	10–20	>20	Class IC: Ventricular proarrhythmia
Flecainide (Tambocor)	—	—	12–27	0.2–1	>1	Propafenone: Dyspnea (2%), worsening of asthma, metallic taste
Propafenone (Rythmol)	—	—	2–10*	0.6–1	—	
Propranolol (Inderal)	0.5	3–5	2–3	0.05–0.1	—	Sinus bradycardia, AV block, depression of LV function (adrenergic-dependent), masked symptoms of hypoglycemia in diabetics
Esmolol (Brevibloc)	<5 min	minutes	0.15	—	—	Sudden discontinuation of β blockers may cause rebound hypertension
Acebutolol (Sectral)	—	24–30	3–4	—	—	
Amiodarone (Cordarone)	1–3 wk	months	26–107 days	0.5–2.5	>2.5	All: Sinus bradycardia; torsades de pointes, heart failure exacerbation
Dronedarone (Multaq)	3–6	—	13–19	—	—	Amiodarone: GI (25%), ocular (10%), CNS, hepatic (40%–55%), dermatologic (15%), hypothyroidism/hyperthyroidism (4%)
Bretium (Bretylol)	—	6–8	5–10	0.5–1.5	—	Dronedarone: N/V/D, asthenia, elevated serum creatinine (51%)
Dofetilide (Tikosyn)	—	—	10	—	—	Dofetilide: Headache (11%), chest pain (10%), dizziness (8%), dyspnea (6%)
Sotalol (Betapace, Betapace AF)	—	—	12	—	—	Ibutilide: Proarrhythmia, nausea, headaches
Ibutilide (Corvert)	—	—	2–12	—	—	
Verapamil (Isoptin)	0.5	6	3–7	0.08–0.3	—	Sinus bradycardia, AV block, negative inotropic effect
Diltiazem (Cardizem)	2–4	4–6	3–6	—	—	
Digoxin (Lanoxin)	0.5–2	≥ 24	30–40	0.5–2 ng/mL	>2.5 ng/mL	VF/VT, N/V as first sign of toxicity
Adenosine (Adenocard)	34 sec (IV)	1–2 min	<10 sec	NA	—	Dyspnea (12%), cough (6%), respiratory failure, bronchospasms (28%), chest pressure (7%), facial flushing (18%)
Moricizine (Ethmozine)	2	10–24	1.5–3.5	NA	NA	All class I agents: Negative inotropic effect, infranodal conduction block
Lidocaine (Xylocaine)	—	0.25	1–2	1.5–6	>7	Class IA: Torsades de pointes
Mexiletine (Mexitil)	—	—	10–12	0.5–2	>2	Class IB: Muscle twitch, seizures, proarrhythmia, dyspnea
Tocainide (Tonocard)	—	—	11–15	4–10	>10	Class IC: Ventricular proarrhythmia
Flecainide (Tambocor)	—	—	12–27	0.2–1	>1	
Quinidine (Quinaglute)	0.5	6–8	6–7	2–6	>8	Quinidine: N/V/D, cinchonism (tinnitus, blurred vision, dizziness, tremor)
Procainamide (Pronestyl)	0.5	≥3	2.5–4.5	4–8	>16	Procainamide: N/V/D (30%), bitter taste, rash, hepatitis, mental depression, psychosis
Disopyramide (Norpace)	0.5	6–7	4–10	40–60	>80	Disopyramide: Anticholinergic effects (dry mouth, blurred vision, urinary retention), hypoglycemia, cholestatic jaundice, agranulocytosis

TABLE 21.6**Antiarrhythmics: Pharmacokinetics and Adverse Reactions—cont'd**

Drug	PHARMACOKINETICS					Adverse Reactions
	Onset (PO) (hr)	Duration (hr)	Half-Life (hr)	Therapeutic Range (mcg/mL)	Toxic Level (mcg/mL)	
Phenytoin (Dilantin)	0.5–1	≥24	22–36	10–20	>20	Phenytoin: Hypotension, gingival hyperplasia, antiepileptic hypersensitivity syndrome
Propafenone (Rythmol)	—	—	2–10*	0.6–1	—	Propafenone: Dyspnea (2%), worsening of asthma, metallic taste
Propranolol (Inderal)	0.5	3–5	2–3	0.05–0.1	—	Sinus bradycardia, AV block, depression of LV function (adrenergic-dependent), masked symptoms of hypoglycemia in diabetics
Esmolol (Brevibloc)	<5 min	minutes	0.15	—	—	Sudden discontinuation of β blockers may cause rebound hypertension
Acebutolol (Sectral)	—	24–30	3–4	—	—	
Bretylium (Bretylol)	—	6–8	5–10	0.5–1.5	—	All: Sinus bradycardia; torsades de pointes, heart failure exacerbation
Sotalol (Betapace, Betapace AF)	—	—	12	—	—	
Amiodarone (Cordarone)	1–3 wk	months	26–107 days	0.5–2.5	>2.5	Amiodarone: GI (25%), ocular (10%), CNS, hepatic (40%–55%), dermatologic (15%), hypothyroidism/hyperthyroidism (4%)
Dronedarone (Multaq)	3–6	—	13–19	—	—	Dronedarone: N/V/D, asthenia, elevated serum creatinine (51%)
Dofetilide (Tikosyn)	—	—	10	—	—	Dofetilide: Headache (11%), chest pain (10%), dizziness (8%), dyspnea (6%)
Ibutilide (Corvert)	—	—	2–12	—	—	Ibutilide: Proarrhythmia, nausea, headaches
Verapamil (Isoptin)	0.5	6	3–7	0.08–0.3	—	Sinus bradycardia, AV block, negative inotropic effect
Diltiazem (Cardizem)	2–4	4–6	3–6	—	—	
Digoxin (Lanoxin)	0.5–2	≥24	30–40	0.5–2 ng/mL	>2.5 ng/mL	VF/VT, N/V as first sign of toxicity
Adenosine (Adenocard)	34 sec (IV)	1–2 min	<10 sec	NA	—	Dyspnea (12%), cough (6%), respiratory failure, bronchospasms (28%), chest pressure (7%), facial flushing (18%)

*Half-life is 6 to 36 hours in patients who are poor metabolizers of propafenone (i.e., patients with low-activity CYP2D6 isozyme).

AV, Atrioventricular; GI, gastrointestinal; LV, left ventricular; NA, not applicable; N/V/D, nausea/vomiting/diarrhea; VF/VT, ventricular fibrillation/ventricular tachycardia; —, none.

episodes of hypotension because of its negative inotropic properties. Overdose with disopyramide may be followed by apnea, loss of consciousness, cardiac arrhythmias, and loss of spontaneous respirations requiring mechanical ventilation or other vigorous treatment modalities. This agent has limited use because of its anticholinergic side effects, including dry mouth, difficulty in urination, dizziness, tachycardia, hyperthermia, and blurred vision.⁴

Class IB

Class IB agents are often used and have less proarrhythmic potential compared with class IA agents. The actions of class IB agents are limited to VAs.

CLINICAL CONNECTION

Lidocaine is often given to treat irritability of the heart resulting from ventricular arrhythmia.

Lidocaine

Lidocaine is used frequently to treat VA occurring during cardiac surgery or after an acute myocardial infarction. After administering IV bolus doses (owing to its short half-life of approximately 1.5 to 2 hours), continuous infusion is necessary to maintain sinus rhythm. Lidocaine is metabolized extensively in the liver to two toxic metabolites, monoethylglycinexylidide and glycinexylidide; these metabolites display antiarrhythmogenic properties but are also highly prone to seizure activity. Patients need to be monitored vigilantly for signs of seizure, such as tremors.³⁰ Other CNS side effects associated with lidocaine are insomnia, drowsiness, ataxia, agitation, and dysarthria. Caution should also be exercised in patients with hepatic failure or CHF because the rate of drug clearance is significantly reduced in either condition. Lidocaine infusions lasting longer than 24 hours may prolong the half-life of lidocaine to approximately 3 hours, leading to a greater risk of lidocaine accumulation and toxicity. In the setting of lidocaine infusion longer than 24 hours, the infusion rate should be reduced

by approximately 50%. Lidocaine has also been implicated in causing respiratory depression and arrest.⁴

Mexiletine

Mexiletine has a mechanism of action similar to lidocaine and is available as an oral formulation. It is indicated for the treatment of life-threatening VAs. Because of its anesthetic properties, it is also used at lower doses to reduce neuropathic pain associated with diabetic neuropathy. In controlled trials, the most frequent adverse events were gastrointestinal disturbances (41%), tremor (12%), and lightheadedness and difficulty in coordination (>10%). Dyspnea and respiratory problems occurred in 5.7% of patients. Coma and respiratory arrest may occur with massive overdoses.³⁰

Tocainide

Tocainide is the oral congener of lidocaine and is used to treat VAs and may also be used to treat myotonic dystrophy and trigeminal neuralgia. Tocainide carries an FDA boxed warning for causing pulmonary disorders, including pulmonary edema, fibrosing alveolitis, pneumonitis, and respiratory arrest (0.11%). These pulmonary manifestations are detectable on radiographic studies within 3 to 18 weeks of therapy. Another boxed warning is for blood dyscrasias, which is not that prevalent (0.18%) but is associated with a fatality rate of up to 25%.⁴

Class IC

Class IC agents are generally not used mainly because of their relatively higher proarrhythmic potential. Other agents from this class have been withdrawn from the market (i.e., encainide and moricizine) because of their substantial proarrhythmic potential, as shown in two landmark trials: Cardiac Arrhythmia Suppression Trial I (CAST I)³¹ and CAST II.³² Class IC agents are commonly used in the management of supraventricular arrhythmias, but they have activity against VAs as well.

Flecainide (Tambocor)

Flecainide (Tambocor) is indicated for the prevention of paroxysmal AF/AFL associated with disabling symptoms and PSVT, including AV nodal reentrant tachycardia, AV tachycardia, other SVT in patients without structural heart disease, and sustained VT. It is efficacious in suppressing AF in 61% to 92% of patients treated. Flecainide has a long half-life, and the dose should not be increased more often than every 4 days. Flecainide was one of the antiarrhythmics studied in CAST in patients with asymptomatic non-life-threatening arrhythmias occurring 6 days to 2 years after documented myocardial infarction. Flecainide contributed to an excessive mortality or nonfatal cardiac arrest rate of 5.1% versus 2.3% for its matched placebo. Long-term oral prophylaxis with an antiarrhythmic agent poses a great risk of adverse events, and relapse rates are high. Also, flecainide elimination is affected by urinary pH, leading to either toxic or subtherapeutic levels. Alkaline pH decreases and acidic pH increases renal excretion of flecainide.⁴

The “pill in the pocket” approach is the alternative treatment of recurrent arrhythmias, in which a pill is taken by the patient at the time of onset of palpitations. One study assessed this approach in the conversion of AF to sinus rhythm with class IC agents, using either flecainide or propafenone as a single oral dose to convert patients to sinus rhythm out of hospital. Flecainide was shown to be equally effective for pill-in-the-pocket treatment of recurrent AF, with a 94% efficacy rate.³³

Propafenone (Rythmol)

Propafenone (Rythmol) seems to be comparable to other antiarrhythmics in preventing PSVT and maintaining sinus rhythm after successful cardioversion. It is considered a first-line agent for conversion of recent-onset (<48 hours) AF, with efficacy rates of 60% to 90%. Therapy is 15% to 30% less effective in patients manifesting symptoms of AF for greater than 48 hours. Propafenone displays nonselective β -blocking activity, and it generally should not be used to treat patients with asthma or bronchospastic disease because β -blocking properties may inhibit bronchodilation. The highest concentrations of the drug are found in the lungs (10-fold higher than in the heart muscles or liver and 24-fold higher than in the kidneys).³⁴

Class II

Class II agents consist mainly of β -blocking agents. These agents are used in the management of hypertension and post-myocardial infarction status; metoprolol is the only agent in this class that may be used in the setting of CHF.

CLINICAL CONNECTION

β blockers should be used with caution in patients with pulmonary disease, especially nonspecific β blockers, as they can have an effect on β agonists used to treat asthma, chronic obstructive pulmonary disease (COPD), and so on.

β Blockers

Propranolol (Inderal), metoprolol (Lopressor), atenolol (Tenormin), and nadolol (Corgard) are available as IV and oral formulations; esmolol (Brevibloc) is available only in the IV form. These agents have negative **dromotropic** activity but are more commonly used for negative chronotropic properties in AF/AFL and to prevent or convert SVT to normal sinus rhythm. β blockers should not be used in settings of acute decompensated heart failure because they can exacerbate symptoms of heart failure. However, after the symptoms of heart failure are stabilized, β blockers may be initiated at lower doses. In settings in which patients with airway disease are overly sensitive to the bronchoconstrictive effects of β blockers, esmolol may be a convenient selection because of its β_1 -selective property. Because of the short half-life of esmolol (approximately 10 minutes), one may titrate the dose to meet the patient's therapeutic and safety goals.

Class III

Class III agents are used to treat supraventricular arrhythmias (SVAs) and ventricular arrhythmias (VAs). Bretylium, which is considered a member of this class, is no longer manufactured in the United States because of a lack of substantial efficacy data.

Amiodarone (Cordarone)

Amiodarone (Cordarone) is effective in the management of VAs and SVAs. In the past, the life-threatening adverse effects of amiodarone prevented it from being used as a first-line agent; it was reserved for patients with life-threatening VAs. Amiodarone seems to exhibit greater efficacy and a lower incidence of proarrhythmic effects than class I or III antiarrhythmics. Today, amiodarone has become a mainstay in the management of AF, VF, and VT.

TABLE 21.7 Routine Laboratory Testing in Patients Receiving Amiodarone

Type of Test	Time When Test Is Performed
Liver enzyme tests	Baseline and then every 6 months
Thyroid function (T ₄ and TSH)	Baseline and then every 6 months
Serum creatinine and electrolytes	Baseline and then every 6 months
Chest radiograph	Baseline and then yearly
Ophthalmic evaluation	Baseline and for visual impairment or symptoms, and then every 6 months
Pulmonary function tests	Baseline and for unexplained dyspnea, especially in patients with underlying lung disease, and if there are suggestive abnormalities on chest radiograph
ECG	Baseline and then yearly

ECG, Electrocardiography; T₄, thyroxine; TSH, thyroid-stimulating hormone.

Amiodarone-induced pulmonary toxicity warrants care when treating patients with arrhythmias. The main caveat associated with amiodarone is its distinctive side effect profile.⁵ Baseline parameters that must be obtained before starting therapy, along with incidences of various side effects, are presented in Table 21.7. Pulmonary toxicity is quite common, as evidenced by cough and by local or diffuse infiltrates on chest radiographs, and occurs at a rate of up to 20%. Amiodarone-induced pulmonary toxicity is managed best by discontinuation or by corticosteroid therapy; in some cases, fatalities of approximately 10% have been reported.³⁰ In addition, amiodarone is regarded as one of the most potent inhibitors of the cytochrome P450 (CYP) 3A4 isoenzyme system, and it inhibits CYP 2C9 and CYP 2C19 (hepatic drug-metabolizing enzymes); concomitant prescription medications, herbals, and over-the-counter (OTC) products must be evaluated for detection of severe, often life-threatening interactions.

Dronedarone (Multaq)

Although similar in chemical structure to amiodarone, dronedarone (Multaq) differs from amiodarone by the removal of the iodine moiety and addition of a methylsulfonamide group. These structural changes result in decreased accumulation of the drug inside various tissues, leading to reduced toxicities of the thyroid gland and other organs associated with amiodarone toxicity (Table 21.8 provides monitoring parameters specifically for dronedarone). In addition, the modifications allow dronedarone to achieve steady state faster than amiodarone due to a shorter half-life of approximately 1 day versus greater than 50 days. Similar to amiodarone, dronedarone is primarily a class III antiarrhythmic, but it shows properties of all four Vaughan Williams classes. It is indicated to reduce risk for hospitalization in patients with paroxysmal or persistent AF/AFL who are currently in sinus rhythm or pending cardioversion to sinus rhythm.³⁵ It is available only for administration via the oral route.

TABLE 21.8 Laboratory Tests in Patients Receiving Dronedarone

Type of Test	Time When Test Is Performed
Liver enzyme tests	Baseline and then periodically during the first 6 months of treatment; then every 6 months
Serum creatinine	Baseline and then 7 days after initiation; then every 6 months
Electrolytes	Baseline and then every 6 months
ECG	Baseline and then every 3 months
Pulmonary function tests	Not necessary unless there is an unexplained dyspnea or nonproductive cough

ECG, Electrocardiography.

Also, similar to amiodarone, Q-T interval prolongation is rare at an incidence of less than 1%. The same precautions taken with amiodarone for risks of Q-T interval prolongation should also be taken with dronedarone therapy based on the ATHENA trial,³⁶ in which dronedarone exhibited a 40% risk of Q-T interval prolongation compared with placebo. Q-T interval prolongation can be monitored by performing 12-lead ECG and measuring the *corrected Q-T interval* (Q-T_c). The Q-T_c takes into account the measurements of all Q-T intervals on the 12-lead ECG. Generally, strong precautions should be taken when the Q-T_c interval exceeds 450 milliseconds (msec); however, therapy should be withheld and alternatives should be considered when Q-T_c exceeds 500 msec.

Similar to amiodarone, this medication is a CYP 3A4 substrate and a moderator inhibitor for both CYP 3A4 and CYP 2D6 isoenzymes. It is contraindicated for use with potent CYP 3A4 inhibitors (e.g., clarithromycin, telithromycin, cyclosporine, itraconazole, voriconazole) and inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin). If used concurrently with nondihydropyridine calcium channel blockers (e.g., diltiazem or verapamil) or β blockers, these medications should be initiated at a lower dose to minimize risk for bradycardia or heart block. Dronedarone is also an inhibitor of P-glycoprotein, and digoxin should be avoided; however, if use of digoxin is necessary, the dose should be empirically reduced by 50% with increased monitoring for clinical response and potential adverse effects.³⁵ A greater than twofold increased risk in mortality was found in patients with New York Heart Association (NYHA) class III and IV CHF, who were treated with dronedarone compared with a placebo in the ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate Severe CHF Evaluating Morbidity Decrease)³⁷ study. Therefore, the drug is contraindicated in any patients with NYHA class IV CHF and NYHA class II-III CHF with recent decompensation requiring hospital admission or referral to a specialized CHF clinic. Other contraindications include Q-T_c greater than 500 msec, HR less than 50 beats/min, concomitant use of Q-T interval-prolonging medications or herbals because of the risk of torsades de pointes, sick sinus syndrome, or second- or third-degree AV block unless a functional pacemaker is present.

Amiodarone and dronedarone are the only two agents in this class of antiarrhythmics. Amiodarone is considered more effective than dronedarone in the management of chronic AF. Current evidence suggests that it would be prudent to continue amiodarone therapy if a patient is tolerating amiodarone, has not developed any adverse effects, and is able to maintain a favorable rhythm. However, the clinician must weigh the risks versus the benefits and the fact that dronedarone is associated with fewer systemic adverse events that lead to discontinuation. In addition, dronedarone may have the same risks of Q-T interval prolongation or even greater risks. The decision to choose one agent over another is based on multiple patient-specific factors.

Providers prescribing dronedarone must enroll in the mPACT Risk Evaluation and Mitigation Strategies (REMS)³⁵ program. This REMS program was developed to halt prescribing of dronedarone to patients in whom the drug may be harmful. This includes patients with permanent AF (in whom cardioversion is not possible) and patients with NYHA class IV or II-III with recent decompensation.

Dofetilide (Tikosyn)

Dofetilide (Tikosyn) is available as an oral formulation and is indicated for the maintenance of sinus rhythm after successful conversion, but it is ineffective in paroxysmal AF. Dofetilide carries a significant risk of Vas, such as torsades de pointes associated with prolongation of the Q-T interval (duration of ventricular electrical activity). The Q-T interval can be reported as Q-T_c. This drug should be discontinued in patients with Q-T_c greater than 500 msec. The risk of torsades de pointes among patients administered dofetilide is greatest for the following patients⁴:

- Women
- Patients with congenital heart disease or ischemic heart disease
- Patients with diminished renal function
- Patients receiving dofetilide doses exceeding 500 mg twice daily

This medication must be adjusted to avoid renal accumulation. Drug interactions with dofetilide pose a significant problem. Agents such as cimetidine, azole antifungals, prochlorperazine, metformin, and the trimethoprim component of trimethoprim-sulfamethoxazole (Bactrim) may inhibit active tubular secretion of dofetilide and increase the plasma concentration. Therapy with dofetilide must be initiated in a facility that can provide continuous ECG monitoring and the presence of personnel trained to manage severe VAs for at least 3 days. Both the prescriber and the pharmacy must be participants in a program known as the *Tikosyn in Pharmacy System (TIPS)* before prescribing and dispensing dofetilide.³⁸

Sotalol (Betapace and Betapace AF)

Sotalol (Betapace and Betapace AF) is available only by the oral route and works by prolonging the AP duration and the relative refractory period. Sotalol can be used for SVAs and VAs. When initiating sotalol, the patient should be kept in a facility that can provide continuous ECG monitoring and the presence of personnel trained to manage severe VAs for at least 3 days.⁴ As with any β -blocking agent, caution must be exercised when treating patients with restrictive airway disease.

Ibutilide (Corvert)

Ibutilide (Corvert) is available as an IV formulation and is an alternative to electrical cardioversion. Ibutilide is the first

antiarrhythmic agent indicated for rapid conversion of AF/AFL of recent onset by the FDA. In clinical trials, ibutilide was more effective for the treatment of AFL than AF (>50% versus <40%). Class I antiarrhythmics and other class III antiarrhythmics should not be given with this medication or within 4 hours of an ibutilide infusion because of the potential for prolonged refractoriness.³⁹ Because AF has the potential to form clots within the atrium of the heart, patients must be adequately anticoagulated before chemical cardioversion to reduce the risk of stroke. Patients who fail electrical cardioversion require lifelong anticoagulation.⁴ There is also evidence (TIME [Timing in Myocardial Infarction Evaluation] study)⁴⁰ to suggest that prophylaxis of magnesium can enhance the efficacy of ibutilide and decrease the incidence of torsades de pointes by greater than 30%. Before initiation, all electrolytes must be maintained within normal limits, and continuous ECG monitoring is required because of the high incidence of VF (2.7%–4.9%).³⁹

Class IV

Calcium Channel Blockers

Only two calcium channel blockers are used in the management of supraventricular arrhythmias and ventricular rate control for AF: verapamil (Isoptin) and diltiazem (Cardizem). These agents exert their effects by blocking calcium channels in the AV node and slowing AV nodal conduction. In contrast to β blockers, verapamil and diltiazem are not favorable agents for use in the setting of CHF; however, they are good alternatives to β blockers in the setting of airway disease.

Miscellaneous

Digoxin (Lanoxin)

Digoxin (Lanoxin) has direct AV-blocking effects and vagotonic properties that aid in reducing the HR. Although digoxin prolongs the relative refractory period of the AV node and reduces the number of impulses through the AV node, it is not regarded as a first-line agent for AF.^{4,30} Digoxin does not have a rapid onset of effect, especially for the management of an acute condition, such as AF; it requires approximately 2 hours to achieve maximal effect. Additionally, digoxin has the potential to shorten the refractory period of atrial muscles, allowing electrical impulses to be conducted throughout the myocardium and ultimately potentiating episodes of AF. It is less effective than β blockers and calcium channel blockers during states of increased sympathetic tone, such as in exercise and stress. Digoxin is not regarded as a first-line agent for the control of ventricular rate in AF except in patients with impaired left ventricular function or heart failure.³⁰

Adenosine (Adenocard)

Rapid administration of adenosine (Adenocard) is implemented to terminate SVTs only. Adenosine has a half-life of approximately 12 seconds, and because of its ultrashort half-life, adenosine is best administered through a central line for rapid arrival at the site of action, or if given through a brachial line, the arm should be held in the upright position followed almost instantly by a saline flush. Dyspnea, hyperpnea, and cough have been reported after administration of IV adenosine in patients with asthma and chronic obstructive pulmonary disease (COPD); these symptoms are generally benign and short lasting.^{41,42}

KEY POINT

Drugs used in advanced cardiac life support included antiarrhythmics; vasopressors, such as epinephrine and vasopressin; the electrolyte magnesium; and atropine for bradycardia or asystole.

Management and Pharmacotherapy of Advanced Cardiac Life Support

Sudden Cardiac Death

Death from heart disease is the leading cause of death in the United States. Of deaths caused by heart disease, nearly three quarters of these result from **sudden cardiac death (SCD)**.⁴³ SCD can be defined as an episode of VF, pulseless VT, pulseless electrical activity (PEA), or asystole, all of which are life-threatening arrhythmias.⁴⁴ Although the fatalities associated with episodes of SCD are unacceptably high, an individual may be resuscitated, and it is common to encounter patients having a “history” of SCD. The goal in treating SCD is to restore sinus rhythm, to prevent further episodes of SCD, and to prevent impairment of neurologic function. Several studies have shown benefits in mortality reduction by minimizing time to defibrillation and by delivery of cardiopulmonary resuscitation (CPR).⁴⁴

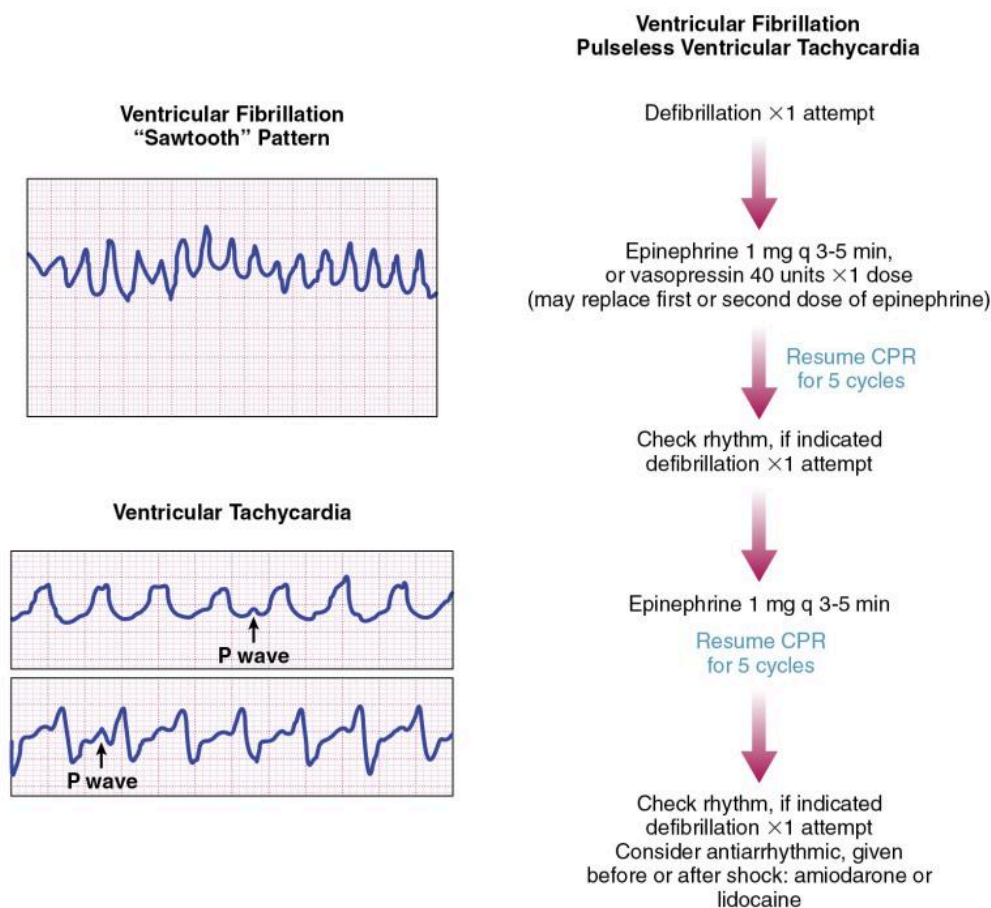
In a patient with VF, survival decreases by 7% to 10% for every minute that passes from the time of symptom onset to

defibrillation.⁴⁴ When CPR is initiated, the decline in survival occurs at a more gradual rate of approximately 3% to 4% for every minute between onset of symptoms and time to defibrillation.⁴⁴ Needless to say, efficient and timely delivery of defibrillation and CPR is imperative for successful management of SCD.

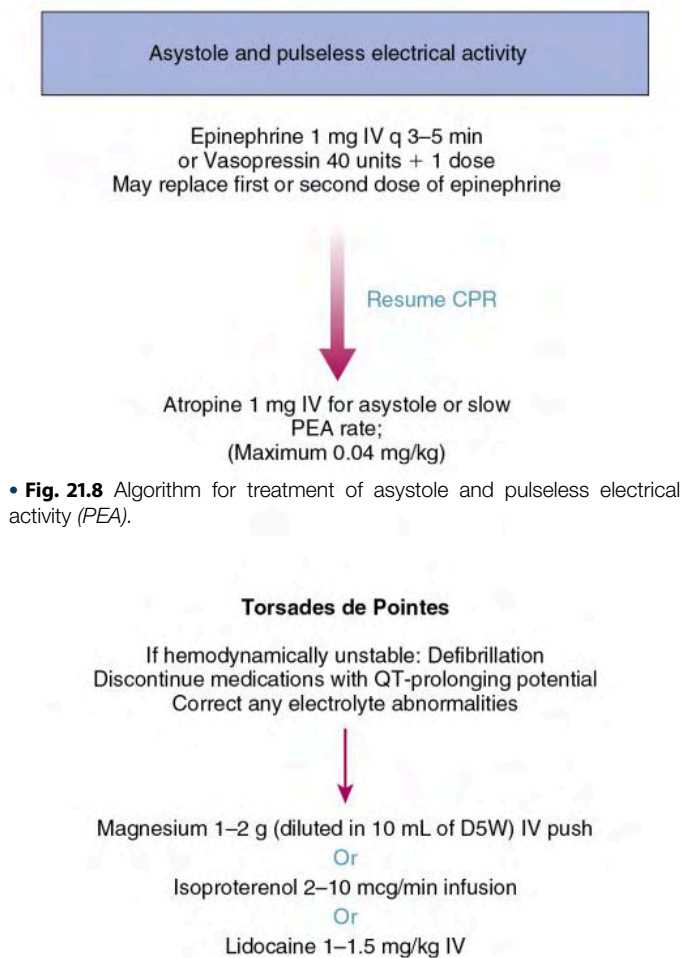
After beginning CPR and attempting defibrillation, health care workers may begin establishing other therapeutic modalities, such as IV access; medication therapy and the insertion of an advanced airway should be considered. VF and pulseless VT are managed primarily by defibrillation and CPR and secondarily by pharmacotherapy; conversely, asystole and PEA are not managed by defibrillation and are managed first by CPR only and second by pharmacotherapy, as depicted in the algorithms in Figs. 21.7, 21.8, and 21.9. It may be prudent to review the national consensus guidelines for further details of advanced cardiac life support algorithms.

Epinephrine

Epinephrine, an endogenous neurotransmitter, is administered in 1-mg doses as a 10-mL solution. Epinephrine stimulates β_1 -adrenergic and β_2 -adrenergic receptors, which are found in dense proportions in the heart and lungs. The effect of epinephrine on α_1 receptors, located within the coronary and cerebral vasculature, is more closely correlated with efficacy. Stimulation of α_1 receptors causes vasoconstriction of the coronary and cerebral vasculature,



• **Fig. 21.7** Left, Ventricular fibrillation pattern and ventricular tachycardia pattern. Right, Algorithm for treatment of ventricular fibrillation and pulseless ventricular tachycardia.



• **Fig. 21.8** Algorithm for treatment of asystole and pulseless electrical activity (PEA).

• **Fig. 21.9** Algorithm for treatment of torsades de pointes. D5W, 5% dextrose in water.

increasing blood flow to the heart's myocardium and the CNS. In contrast, stimulation of β_1 receptors increases HR, resulting in increased O_2 demand on the heart and impairing O_2 delivery to the myocardium and the CNS.

One main caveat associated with epinephrine use is the occurrence of decreased receptor affinity in the setting of metabolic acidosis. Metabolic acidosis may readily ensue during SCD because of hypoxic conditions leading to a shift in anaerobic respiration. At the present time, there is no recommended maximal dose of epinephrine in the management of SCD. Postresuscitation side effects include hypertension and tachycardia.

Vasopressin

Vasopressin, also known as *antidiuretic hormone*, is an endogenous hormone that acts as a potent vasoconstrictor. Before 2015, Vasopressin was administered as a one-time IV dose of 40 units. Because the effects of vasopressin have not been shown to be exceedingly different from the effects of epinephrine, this dose was to be administered in lieu of the first or second dose of epinephrine when treating any form of SCD.⁴⁴ More recently, vasopressin was removed from the algorithm because of lack of benefit over epinephrine.⁴⁵ In contrast to epinephrine, vasopressin is a nonadrenergic vasoconstrictor;

its vasoconstricting properties manifest as activation of V_1 receptors, which are found in the vasculature. Once stimulated, V_1 receptors release Ca^{2+} from the sarcoplasmic reticulum in vascular smooth muscle, leading to vasoconstriction and increasing SVR and coronary and cerebral blood flow. In contrast to epinephrine, vasopressin receptor affinity is not compromised in the setting of metabolic acidosis. In the setting of long-term continuous infusion therapy, vasopressin may cause gastrointestinal and skin ischemia; however, in the setting of SCD, these adverse events would be unlikely.

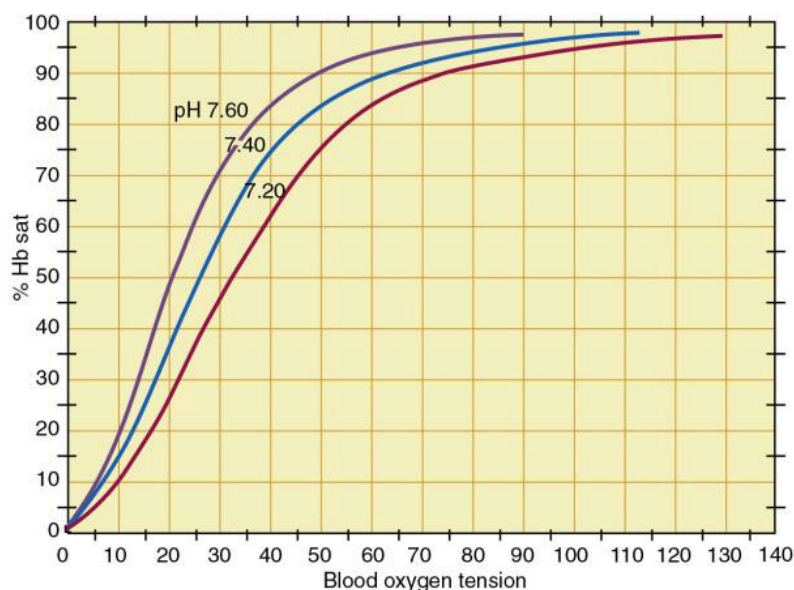
Atropine (AtroPen)

Atropine (AtroPen) is indicated for certain forms of SCD, such as asystole or PEA, usually given at a dose of 1 mg as IV push, along with epinephrine or vasopressin. Atropine acts by blocking the actions of acetylcholine, an endogenous cholinergic agent. The cholinergic system is typically involved in HR reduction, and by blocking this effect, atropine exerts a pronounced (albeit short-lived) chronotropic effect on the heart. The recommended maximal dose of atropine used during resuscitation is 0.04 mg/kg. Because atropine affects acetylcholine globally within the body, noticeable adverse effects include mydriasis, dry mouth, urinary retention, and constipation.

Sodium Bicarbonate

Sodium bicarbonate ($NaHCO_3$) is routinely and frequently used for the management of metabolic acidosis. It is indicated in a variety of settings that may induce acidemia, including metabolic acidosis from severe renal disease, shock, cardiac arrest, uncontrolled diabetes, extracorporeal circulation of blood, severe diarrhea, or certain drug intoxications, such as with tricyclic antidepressants, barbiturates, and salicylates.⁴⁶ The current Surviving Sepsis Guidelines⁵ do not endorse $NaHCO_3$ infusions for hypoperfusion-induced lactic acidosis unless acidosis is severe (i.e., pH <7.15) because of a lack of evidence supporting its benefit.⁴⁷ Furthermore, several studies in patients with diabetic ketoacidosis (DKA) have shown no decrease in time to resolution of acidemia with administration of $NaHCO_3$.⁴⁸ However, adverse effects of $NaHCO_3$ infusions include fluid overload resulting from the Na^+ content (1 mL of 4.2% $NaHCO_3$ contains 11.5 mg of Na^+ ; 1 mL of 8.4% $NaHCO_3$ contains 22.9 mg of Na^+), a decrease in serum Ca^{2+} , and elevations in carbon dioxide (CO_2) caused by the conversion of $NaHCO_3$ to CO_2 .⁴⁶ Because of the increase in CO_2 that occurs with $NaHCO_3$ infusions, patients must be on adequate ventilatory support. Despite these concerns, critical care practitioners frequently utilize $NaHCO_3$ infusions for management of severe acidosis.

Treatment of metabolic acidosis should first and foremost involve correction of the underlying cause of acidosis. When administering bicarbonate infusions, the goal of therapy should be to normalize serum $NaHCO_3$ levels. Symptoms of acidemia and serum pH (goal pH of 7.2) should be considered in determining whether $NaHCO_3$ infusion is necessary. The package insert lists a standard dose of $NaHCO_3$ at 2 to 5 mEq/kg. Most drug references recommend replacement of 50% of total $NaHCO_3$ dose over 3 to 4 hours followed by the remainder of the dose over 8 to 24 hours.^{1,4,30} To avoid the overcorrection of acidemia, the initial



• **Fig. 21.10** Bohr effect. (From Kacmarek, R. M., Wilkins, R. L., Stoller, J. K., et al. [2013]. *Egan's fundamentals of respiratory care* [10th ed.]. St. Louis, Missouri: Mosby.)

goal of NaHCO_3 administration should be to lower the serum NaHCO_3 by 10 to 12 mEq/L, rather than to normalize the serum NaHCO_3 level. Full correction of CO_2 may cause rebound acidosis because there is a delay in ventilation readjustment to CO_2 levels. Although NaHCO_3 infusions can be prepared in several diluents, including 5% dextrose in water (D5W) or normal saline, preparation in normal saline increases risk of developing hypernatremia. In patients with cardiac arrest and acidosis, undiluted bicarbonate can be given as an IV push at a dose of 0.5 to 1 mEq/kg of body weight.⁴⁶

The presence of carbon dioxide helps the release and delivery of O_2 from hemoglobin, also known as the **Bohr effect**. When comparing the O_2 dissociation curves of a serum sample with CO_2 and another with no CO_2 , O_2 is able to dissociate more readily in the former state, as depicted in Fig. 21.10.

In addition, NaHCO_3 decreases hydrogen ion (H^+) concentration in the serum by reacting with it, yielding carbon dioxide and water. For this reaction to continue, the product (CO_2) must be removed. NaHCO_3 therapy aids in increasing extracellular pH only if ventilation is sufficient to remove the CO_2 . If *hypercapnia* (excess CO_2 in blood) ensues, as CO_2 accumulates in serum, it eventually crosses cellular membranes readily; intracellular pH may continue to decline, and further deterioration of cellular function occurs.

Magnesium Sulfate

Magnesium is often implemented in the management of torsades de pointes. Although its mechanism has not been fully elucidated, magnesium may exert its pharmacologic effect by prolonging conduction time; however, its role has been clearly delineated. IV magnesium may be effective whether or not a patient is *eumagnesemic* (having a normal serum magnesium level). The typical dose consists of 1 to 2 g and may be repeated, separated by several minutes. No maximal dose of magnesium has been determined as yet; however, patients with normal renal function are reported to tolerate up to 16 g in a 24-hour period. A continuous infusion regimen may be initiated at a rate of 0.5

to 1 g/hr. Caution is warranted when treating patients with renal insufficiency. Signs and symptoms of magnesium intoxication include the following:

- Sweating
- Hypotension
- Hypothermia
- Depression of reflexes
- CNS depression

Severe hypermagnesemia may result in respiratory depression or fatal respiratory paralysis, circulatory collapse, and flaccid paralysis. Absence of patellar reflex is a clinical sign of magnesium intoxication.

Alternative Routes of Medication Administration

Intraosseous Route

In the face of life-threatening medical emergencies in which there is a dire need for medication and fluid delivery, it is incumbent on the health care worker to provide vascular access in the most efficient and safest way possible. Often IV access is difficult, if not impossible, in infants and young children, older patients with circulatory collapse, and IV drug abusers. In such situations, an intraosseous (IO) needle may be inserted with relative ease, even in the most poorly perfused patients. The 2010 American Heart Association guidelines⁴⁴ for CPR and emergency cardiovascular care recommend IO therapy as an alternative to direct IV therapy.

The marrow of IO bone provides a rich network of vessels that ultimately drains into the central circulation, allowing medications and fluids to gain almost instant access to the central circulation. IO access is recommended for use in children and adults. IO access may be problematic when implemented in older patients because of the presence of a thicker cortex of bone and smaller marrow cavity; inability to enter the marrow may increase the risk

of bone fracture. Typically, an IO needle should not remain at the site of insertion for greater than 3 to 4 hours.

CLINICAL CONNECTION

The acronym NAVE_L (**N**aloxone, **A**tropine, **V**asopressin, **E**pinephrine, **L**idocaine) is used for agents that can be used for endotracheal delivery.

Endotracheal Route

In the event that the IV route is inaccessible, a few agents are amenable to endotracheal delivery; these agents have come to be known by the acronym NAVE_L:

Naloxone
Atropine
Vasopressin
Epinephrine
Lidocaine

The following should be done when administering the previously listed agents by the endotracheal route:

- The patient should be placed in the supine position, as opposed to the Trendelenburg position, and chest compressions should cease.
- A catheter should be inserted into the endotracheal tube and allowed to pass the tip of the tube. The medication solution should be sprayed down the tube, followed by 5 to 10 rapid ventilations with a respirator bag.
- Medications should be diluted with approximately 10 mL of distilled water or normal saline. Endotracheal absorption is greater with distilled water, but distilled water has a negative effect on the partial pressure of oxygen. Generally, the systemic absorption of these medications is reduced via the endotracheal route, and the dose administered should always be 2 to 2.5 times the usual IV dose, except for vasopressin; the vasopressin IV dose of 40 U may be given via the endotracheal route.

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. In which phase of the cardiac cycle does ventricular contraction occur?
2. Identify three functions that regulate MAP.
3. Which measurements, taken by a pulmonary artery catheter, are estimates of the intravascular volume?
4. Hypotension is first managed by what mode of therapy?
5. What vasopressor acts only on the α receptors within the vasculature?
6. Which agents exert an inotropic effect on the heart?
7. What electrolyte abnormality may potentiate the adverse effects of digoxin?
8. What drug should be given for the management of extravasation caused by vasopressors?
9. What Vaughan Williams class of antiarrhythmics acts on the fast Na⁺ channels in the myocardium?
10. What antiarrhythmic agent is structurally similar to amiodarone but has an improved side effect profile?

11. In patients taking dofetilide, at what Q-T_c interval should the drug be discontinued because the risk for torsades de pointes becomes too great?
12. Which antiarrhythmic agent is highly associated with the development of SLE?
13. Identify the four categories of SCD.
14. What medication is indicated for treatment of asystole and pulseless electrical activity but not ventricular fibrillation or pulseless VT during cardiac arrest?
15. What are the two alternative routes of medication administration during cardiac arrest when an IV route is not available?
16. In a patient with septic shock, what is the pH in which the Surviving Sepsis Guidelines recommend utilizing NaHCO₃ therapy?
17. When medications are administered via the endotracheal route during cardiac arrest, the dose should be increased by how many times the usual IV dose?

CLINICAL SCENARIO 1

Answers can be found in [Appendix A](#).

A.M., a 28-year-old female, was rushed to the emergency department of a local hospital by paramedic staff after she collapsed suddenly at work. When she collapsed, the staff in her office called for an ambulance, but basic life support was not started. It was reported that she was in ventricular fibrillation when the paramedic staff arrived at the scene. The paramedics promptly administered two shocks with a defibrillator, and after the second shock a pulse could be felt. On arrival at the hospital, the patient's blood pressure dropped to 85/42 mm Hg, and the cardiac monitor showed supraventricular tachycardia of 170 beats/min. The patient was admitted to the intensive care unit for management of hypotension.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

CLINICAL SCENARIO 2

Answers can be found in [Appendix A](#).

R.W., a 49-year-old man, is visiting his mother, who had been admitted to a nursing home for long-term rehabilitation because of a spinal cord injury. He goes to the bathroom, and a few minutes later his mother hears a loud thud; she calls out to him, but there is no response. After an additional 3 minutes, the head nurse and the clinical pharmacist find R.W. lying in the bathroom, initiate CPR, and obtain the code cart. The initial electrocardiography (ECG) reading reveals pulseless electrical activity, and one dose each of epinephrine and atropine is given as a rapid IV push, followed by a saline flush. The code team arrives to continue CPR, and a subsequent ECG reading reveals ventricular fibrillation. One shock is delivered, and a dose of amiodarone 300 mg IVPB (intravenous piggyback) over 10 minutes is administered. The patient regains consciousness and becomes hemodynamically stable.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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22

Drugs Affecting Circulation: Antihypertensives, Antianginals, Antithrombotics

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CHAPTER OUTLINE

Hypertension

Epidemiology and Etiology
2020 and 2021 Management of Hypertension Guidelines Update
Pathophysiology
Hypertensive Crisis

Hypertension Pharmacotherapy

Angiotensin-Converting Enzyme Inhibitors
Angiotensin II Receptor Blockers
Direct Renin Inhibitors
Calcium Channel Blockers
 β Blockers
Diuretics
 Potassium-Sparing Diuretics
 Thiazide and Thiazide-Like Diuretics
 Loop Diuretics
Aldosterone Antagonists
Centrally Acting Adrenergic Agents
 α_1 -Adrenergic Antagonists
Antiadrenergic Agents
Vasodilators

Angina

Epidemiology, Etiology, and Pathophysiology
Pharmacotherapy
 Nitrates
 Ranolazine

Antithrombotic Agents

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 Potential Reversal Agents for Direct Oral Anticoagulants
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 Cilostazol (Pletal) and Pentoxifylline (Trental)
 Vorapaxar (Zontivity)
 Glycoprotein IIb/IIIa Inhibitors
Thrombolytic Agents

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to drugs affecting circulation: antihypertensives, antianginals, and antithrombotics
2. Categorize the stages of normal to high blood pressure
3. Define a hypertensive crisis and differentiate between hypertensive emergency and hypertensive urgency
4. Design an algorithm for the pharmacotherapy of hypertension
5. Compare and contrast the clinical pharmacology of the agents used for hypertensive pharmacotherapy
6. Describe the chronotherapeutic effect of blood pressure and design a pharmacotherapy regimen based on this principle
7. Describe the mechanism of action of angiotensin-converting enzyme inhibitors, calcium channel blockers, and β blockers

8. Compare and contrast the clinical pharmacology of spironolactone and eplerenone
9. List drug–drug interactions relevant to antihypertensives and plausible mechanisms
10. Describe the formation and elimination of an acute coronary thrombus
11. Describe the pathophysiology of angina and the drugs used to treat angina
12. List the agents in each of the following antithrombotic classes: anticoagulants, antiplatelets, and thrombolytics
13. Describe the mechanism of action of warfarin, direct oral anticoagulants (DOACs), heparin and low-molecular-weight heparin (LMWH)
14. Compare and contrast the clinical pharmacology of heparin and LMWH
15. Describe clinical pharmacology of DOACs
16. List the laboratory parameters that may be used to monitor for the effect of heparin, LMWH, and direct thrombin inhibitors
17. Describe the mechanism of heparin-induced and warfarin-induced paradoxical thrombosis
18. Compare and contrast the clinical pharmacology of aspirin, clopidogrel, ticlopidine, and dipyridamole
19. Describe the role of genetic polymorphism in the antiplatelet activity of clopidogrel and anticoagulant effect of warfarin
20. Describe the indication and mechanism of action of glycoprotein IIb/IIIa inhibitors
21. List the indications and contraindication of thrombolytic agents

KEY TERMS AND DEFINITIONS

Antithrombotics Drugs that prevent or break up blood clots in conditions such as thrombosis or embolism; antithrombotics include anticoagulants, antiplatelets, and thrombolytics.

Arterial blood pressure (blood pressure) Defined hemodynamically as the product of systemic vascular resistance and cardiac output (heart rate $\times$ stroke volume).

Cardiovascular disease (CVD) Damage to the heart and the blood vessels or circulation, including to the brain, kidney, and the eyes.

Chronotropic Influencing the rate of rhythmic movements (heartbeat).

Circadian rhythm Human biologic variations of rhythm within a 24-hour cycle.

Creatinine clearance (CrCl) Measurement of the renal clearance of endogenous creatinine per unit of time; approximates glomerular filtration rate (GFR) but overestimates GFR by 10% to 15%; used for drug dosage guidelines.

D-dimers Covalently cross-linked degradation fragments of the cross-linked fibrin polymer during plasmin-mediated fibrinolysis; level increases after the onset of fibrinolysis and allows for identification of the presence of fibrinolysis.

Dose-ceiling effect Maximum dose of a drug, beyond which it no longer exerts a therapeutic effect; however, its toxic effect increases.

Fibrin split or fibrinogen degradation products (FDPs) Small peptides that result after the action of plasmin on fibrinogen and fibrin in the fibrinolytic process. FDPs are anticoagulant substances that can cause bleeding if fibrinolysis becomes uncontrolled and excessive.

Glomerular filtration rate (GFR) Volume of water filtered from the plasma by the kidney via the glomerular capillary walls into Bowman capsules per unit time; considered to be 90% of creatinine clearance and equivalent to insulin clearance.

Hypertensive emergency Blood pressure greater than 180/120 mm Hg, with the elevation of blood pressure accompanied by acute, progressing target organ injury.

Hypertensive urgency Blood pressure greater than 180/120 mm Hg without signs or symptoms of acute target organ complications.

Inotropes Drugs influencing the contractility of a muscle (heart).

Intrinsic sympathomimetic activity (ISA) Having the ability to activate and block adrenergic receptors, producing a net stimulatory effect on the sympathetic nervous system.

Renin Enzyme, also known as angiotensinogenase, released by the kidney in response to a lack of renal blood flow and responsible for converting angiotensinogen into angiotensin I.

Substitute neurotransmitters Neurotransmitter or hormone replacements that may be weaker or inert.

The circulatory system comprises an integral functional part of the cardiopulmonary system. Drug therapy affecting the circulation is seen in the acute critical care, outpatient care, and home care environments. This chapter presents three classes of drug therapy targeted at the circulatory system. After a brief review of the epidemiology, etiology, and pathophysiology of hypertension, the multiple drug groups used as antihypertensives are described. Drugs used to treat angina pectoris are the second group of drugs described. The third group of agents affecting circulation, antithrombotics, comprises several classes of drugs used to regulate clotting mechanisms.

Hypertension

KEY POINT

Normal blood pressure is defined as blood pressure of less than 120/80 mm Hg. The diagnosis of hypertension and goal blood pressure are based on individual risk factors.

Epidemiology and Etiology

Between 2017 to 2018, it was estimated that almost half of the population (~49.6%) in the United States had hypertension (defined as blood pressure [BP] $\geq$ 130/80 mmHg). For patients with known hypertension on antihypertensive therapies, less than half (~39.6%) had BP within target range. On a global scale, more than 1 billion people over the age of 30 have hypertension, with less than half of this population aware of their diagnosis. Additionally, only 20% of the population diagnosed hypertension have their BP under control.^{1,2} Hypertension adversely affects numerous body organs, including the heart, brain, kidney, and eyes. Damage to these organ systems resulting from hypertension is termed end organ damage (e.g. **cardiovascular disease [CVD]**). Uncontrolled hypertension increases CVD morbidity and mortality by increasing the risk of developing left ventricular hypertrophy, angina, myocardial infarction (MI), heart failure, stroke, peripheral arterial disease, retinopathy, and kidney disease. One

of eight deaths can be attributed to hypertension, and the World Health Organization reports that suboptimal blood pressure (systolic blood pressure [SBP] above 115 mm Hg) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease. Blood pressure increases with age, and hypertension is more prevalent in adults older than 65 years. This fact is of great concern because it is estimated that by 2040, 25% of the American population will be older than 65. Hypertension occurs more frequently in men than in women and occurs in more patients of African American descent than those of Caucasian descent. Evidence suggests that individuals who are normotensive have a greater than 90% lifetime risk for developing hypertension by age 55.³

2020 and 2021 Management of Hypertension Guidelines Update

The 2020 International Society of Hypertension (ISH) Global Hypertension Practice Guidelines and the 2021 guidelines for the pharmacological management of hypertension in adults compiled by the World Health Organization (WHO) are the most up-to-date guidelines for the management of hypertension.^{4,5} Both guidelines addressed thresholds for pharmacologic treatment, agents of choice for hypertension management, and treatment goals for various hypertensive populations. The ISH guideline defines hypertension as blood pressure $\geq 130/85$ mm Hg, and hypertension was classified into three categories based on patients' blood pressure (Table 22.1).

Blood pressure targets varied based on patients' comorbidities and risks for cardiovascular diseases. For patients with hypertension and no other comorbidities, both the ISH and WHO guidelines recommend targeting BP of $<140/90$ mmHg. If the targeted BP could not be achieved, the ISH guideline recommends reduction of at least 20 mmHg in systolic and/or 10 mmHg in diastolic BP from patients' baseline. Patients less than 65 years of age should optimally aim for a BP of $<130/80$ mmHg, if tolerated. For patients with hypertension and other comorbidities (e.g. coronary artery disease, stroke, heart failure, etc), both the WHO and ISH recommends lowering SBP to <130 mmHg. The ISH further recommends targeting DBP of <80 mmHg for patients with hypertension and other comorbidities and BP target of $<140/90$ mmHg for the elderly population^{4,5} (Table 22.2).

Based on the ISH guidelines, pharmacological therapy is recommended in a patient with grade 2 hypertension or grade 1 hypertension with comorbidities. The WHO guideline recommends initiation of pharmacological therapy if BP is $>140/90$ mmHg for patients without comorbidities or if BP is $>130/80$ mmHg for patients with comorbidities. The patient should be followed up in 1 to 3 months for blood pressure check. For a patient with severe hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg), pharmacological management should be initiated immediately.^{4,5}

TABLE 22.1 Classification of Hypertension Based on Blood Pressure⁴

Category	Systolic Blood Pressure		Diastolic Blood Pressure
High Normal	130 to 139 mmHg	AND/OR	85 to 89 mmHg
Grade 1	140 to 159 mmHg	AND/OR	90 to 99 mmHg
Stage 2	≥ 160 mmHg	AND/OR	≥ 100 mmHg

In contrast to previous guidelines, which recommended initiating therapy with a single agent, the current guidelines recommend initiating with combination therapy, preferably as a single pill. The ISH guidelines recommend calcium channel blockers (CCBs) along with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) as initial combination therapy for patients not of African descent. If patients could not achieve their target BP after 3 months of therapy, health care practitioners should consider adding on thiazide-like diuretics. For patients of African descent, initial combination therapy of CCBs plus thiazide-like diuretics or CCBs plus ARBs is preferred. Beta blockers may be prescribed in patients with indications, such as heart failure or atrial fibrillation. The WHO guideline recommends initiating combination therapy with any of the three aforementioned drug classes.^{4,5} Blood pressure medication doses and agents should be adjusted to achieve target blood pressure (Table 22.3). If goal blood pressure is not achieved within a month of initiation of drug therapy, increasing the dose of the initial antihypertensive combination therapy is warranted. If goal blood pressure is still not achieved, titrate medication dosages up and add a third antihypertensive agent. Antihypertensives from nonpreferred medication classes can be used if target blood pressure cannot be achieved despite use of three antihypertensives or in the presence of contraindications to preferred medication classes.⁴

KEY POINT

When the cause is unknown, hypertension is termed *primary* or *essential* hypertension.

In almost all cases, the etiology of hypertension is unknown, and it is termed either *primary hypertension* or *essential hypertension*. The prevalence of secondary hypertension is less than 10%; secondary hypertension includes many disease-induced and drug-induced etiologies. Disease-induced causes of hypertension include Cushing syndrome, hyperparathyroidism, hyperthyroidism, pheochromocytoma, primary aldosteronism, and kidney disease. Drug-induced causes of hypertension include amphetamines, corticosteroids, cyclosporine, erythropoietin, estrogens, nonsteroidal antiinflammatory drugs (NSAIDs) including cyclooxygenase-1 inhibitors (e.g., ibuprofen and naproxen) and cyclooxygenase-2 inhibitors (e.g., celecoxib), pseudoephedrine, sibutramine, tacrolimus, venlafaxine, high sodium-containing over-the-counter (OTC) products

TABLE 22.2 Target Blood Pressure by Age and Comorbidities

Patient Population	Target Blood Pressure
No comorbidities <65 years	SBP <140 mm Hg DBP <90 mm Hg
No comorbidities ≥ 65 years	SBP <130 mm Hg DBP <80 mm Hg
Comorbidities <65 years	SBP <130 mm Hg DBP <80 mm Hg
Comorbidities ≥ 65 years	SBP <140 mm Hg DBP <90 mm Hg

DBP, diastolic blood pressure; SBP, systolic blood pressure; ASCVD, atherosclerotic cardiovascular disease.

TABLE 22.3 Titration of Antihypertensive Agents to Achieve Target Blood Pressure

Strategy A	- Start with <i>two</i> antihypertensive medications (CCB plus ACEI or ARB, if not of African descent) - CCB plus thiazide-like diuretics or CCB plus ARB, if of African descent - Beta blockers for specific indications (e.g., heart failure, atrial fibrillation) - If goal BP is not achieved: titrate doses of both medications as necessary - If goal BP is still not achieved: add a third agent, such as thiazide-like diuretics and titrate dose to maximum as necessary to achieve target BP
Strategy B	- Start with <i>two</i> antihypertensive medications (any combination of CCB, ACEI or ARBs, or thiazide-like diuretics) - If goal BP is not achieved: titrate doses of both medications as necessary - If goal BP is still not achieved: add a third agent and titrate dose to maximum as necessary to achieve target BP

BP, Blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

(e.g., Alka-Seltzer effervescent antacid tablets), OTC weight loss products (e.g., ephedrine-containing diet pills), and chronic alcohol ingestion.^{6,7}

Pathophysiology

KEY POINT

Arterial blood pressure is a product of systemic vascular resistance and cardiac output ([heart rate] × [stroke volume]).

Arterial blood pressure, termed **blood pressure**, is generated by the interplay between blood flow and the resistance to blood flow. Arterial blood pressure reaches a peak during cardiac systole and a nadir at the end of diastole. Arterial blood pressure is defined hemodynamically as the product of cardiac output (heart rate × stroke volume) and total peripheral resistance. Venous capacitance, which affects the volume of blood (*preload*), is a major determinant of cardiac output and SBP. Arteriolar capacitance (*afterload*) is a major determinant of total peripheral resistance and DBP. Antihypertensives elicit actions on some or all of the hemodynamic parameters that define arterial blood pressure.

Hypertensive Crisis

KEY POINT

Hypertensive crisis is defined as systolic blood pressure (SBP) 180 mm Hg or greater and diastolic blood pressure (DBP) 120 mm Hg or greater, encompassing both hypertensive emergency and urgency.

A patient with blood pressure greater than 180/120 mm Hg is considered to be in a hypertensive crisis. A hypertensive crisis represents either a hypertensive urgency or a hypertensive emergency. A **hypertensive urgency** usually signifies high blood pressures without signs or symptoms of acute target organ complications;

however, patients may present with severe headaches, shortness of breath, nosebleeds, or severe anxiety. In these situations, improvement in blood pressure control can be accomplished over a period of 24 to 48 hours.⁸ Overaggressive use of intravenous drugs and oral medications can cause too rapid a decrease in blood pressure. Rapid decrease in blood pressure can result in hypoperfusion of organs such as the brain, kidneys, and heart. Oral antihypertensive agents such as captopril, clonidine, and labetalol are routinely used to manage hypertensive urgencies, followed by close observation for several hours. Patients can benefit from antihypertensive medication adjustments, if they are found to be noncompliant with taking their medications.

A **hypertensive emergency** exists when the elevation of blood pressure is accompanied by acute progressing target organ injury. Examples of acute target organ injury include encephalopathy, intracranial hemorrhage, severe retinopathy, renal failure, unstable angina, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, and eclampsia. Hypertensive emergencies require admission to an intensive care unit, invasive arterial blood pressure monitoring, and immediate but gradual blood pressure reduction over minutes to several hours with intravenous antihypertensives. The initial goal is to reduce blood pressure by no more than 25% within 1 hour after starting therapy.⁹

In the next 2 to 6 hours, the blood pressure must be gradually decreased to 160/100 to 110 mm Hg. If the decreased blood pressure is well tolerated by the patient, further reduction of blood pressure toward normal can be attempted over the next 24 to 48 hours. Recommendations differ for patients with severe preeclampsia or eclampsia, aortic dissection, or pheochromocytoma crisis. For this patient population, SBP should be reduced to <140 mmHg within the first hour (<120 mmHg for pheochromocytoma crisis). In patients with ischemic stroke who are to receive IV fibrinolytic therapy, SBP should be lowered to <185 mmHg and DBP to <110 mmHg before initiation of fibrinolytic therapy.⁹ Intravenous nicardipine, clevidipine, labetalol, and nitroprusside can be used to manage most types of hypertensive emergencies. Depending on other comorbid conditions, alternative intravenous medications can be employed (e.g., nicardipine, esmolol, nitroglycerin, ACEI, and hydralazine). Nitroprusside at high doses or when used for long durations can cause methemoglobinemia. Classic methemoglobin blood is chocolate brown and is without color change despite exposure to air.

Hypertension Pharmacotherapy

KEY POINT

First-line drug groups used to treat hypertension include thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs).⁴

KEY POINT

Second-line antihypertensives include α_2 agonists, vasodilators, β blockers, α and β blockers, direct renin inhibitors (DRIs), and antiadrenergic agents.⁹

Angiotensin-Converting Enzyme Inhibitors

ACEIs act primarily through suppression of the renin-angiotensin-aldosterone system (RAAS). Because of a lack of renal blood flow, **renin** is released into the circulation, where it acts on angiotensinogen to produce angiotensin I. In the pulmonary

vasculature, angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II is a highly potent endogenous vasoconstrictor that also stimulates aldosterone secretion from the zona glomerulosa cells of the adrenal cortex, contributing to sodium and water retention.¹⁰ Angiotensin II also stimulates the release of catecholamines from the adrenergic nerve endings and mediates the release of central sympathetic outflow. ACE is abundant in the endothelial cells of blood vessels and, to a lesser extent, in the kidneys.

ACEIs block the conversion of angiotensin I to angiotensin II by competing with the physiologic substrate angiotensin I for the active site of ACE (Fig. 22.1). The affinity of ACEIs for ACE is approximately 30,000 times greater than for angiotensin I. ACEIs also inhibit kininase, which is responsible for the degradation of bradykinin and other vasodilating substances, including prostaglandin E₂ (PGE₂) and prostacyclin (PGI₂), which enhances the antihypertensive effects of these drugs. Because ACEIs are potent antihypertensives in patients with low-renin hypertension, the effects on bradykinin may have an integral role in the mechanism of action of these agents. The hemodynamic effects of ACEIs are a reduction of peripheral arterial resistance, an increase in cardiac output, little or no change in heart rate, an increase in renal blood flow, and unchanged **glomerular filtration rate (GFR)**. ACEIs have mild antihyperlipidemic effects.

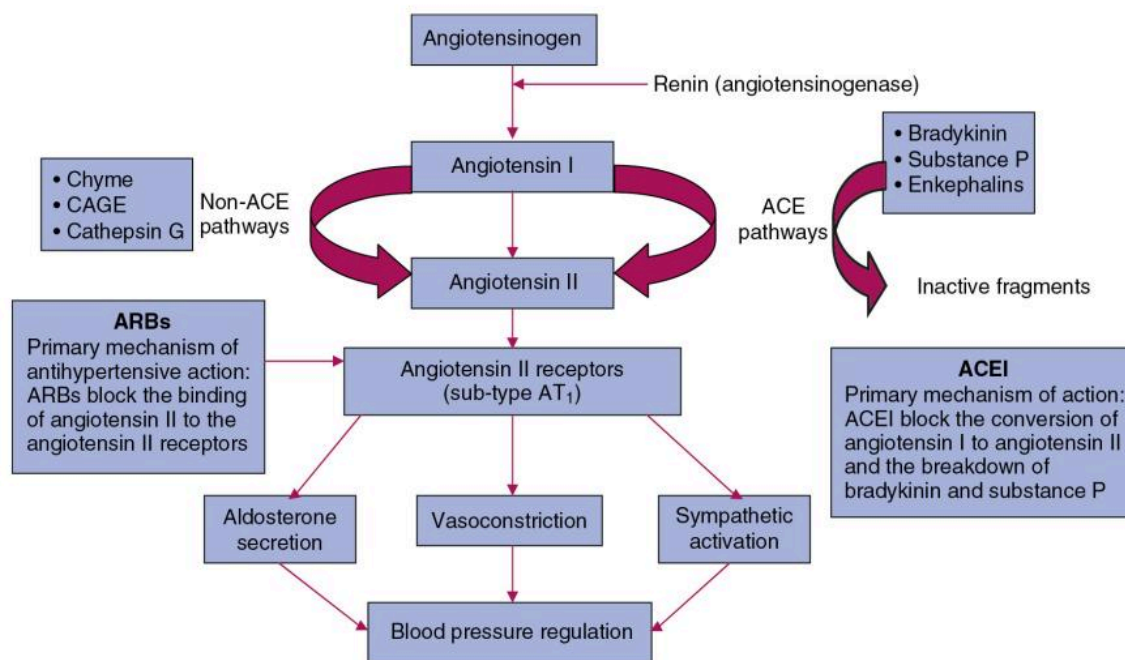
Ten ACEIs are available in the United States. ACEIs and ARBs are the preferred antihypertensives in the setting of CKD. ACEIs generally decrease SBP and DBP by 15% to 25%. ACEIs are most effective in normal-renin or high-renin hypertension; however, they are also effective in low-renin hypertension, especially when used at maximal doses. ACEIs are effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

ACEIs are homogeneous, which means there is very little variability among ACEIs in terms of efficacy and toxicity. In contrast to β blockers and thiazide diuretics, ACEIs do not induce glucose

intolerance, hyperlipidemia, or hyperuricemia. With the exception of captopril, all ACEIs are generally administered once or twice daily. Enalaprilat is the only available parenteral ACEI. Table 22.4 presents the pharmacokinetics and dosage guidelines for ACEIs.¹¹

The most common adverse effect associated with ACEIs is a persistent nonproductive dry cough (20%–30%). The cough may be due to ACEI-induced accumulation of kinins, prostaglandins, or substance P in the respiratory tract. The cough may develop within days to 1 year after the start of therapy. Antitussives are ineffective in relieving ACEI-induced cough. Cross-reactivity among the ACEIs is absolute; however, ARBs rarely cause cough and may be considered an alternative. ACEI-induced rash is also common; the incidence is 10%, and the reaction is usually transient. The rash often occurs in the upper and lower extremities and is often accompanied by pruritus and erythema. A higher incidence of rash with captopril relative to other ACEIs may be due to the sulfhydryl-containing structure of captopril. All other ACEIs, with the exception of fosinopril (phosphorus-containing), possess a dicarbonyl group. ACEIs are known to cause dysgeusia (6%), manifesting as a metallic or salty taste or loss of taste perception.

ACEIs may cause a slight increase in potassium that is generally inconsequential. The risk of hyperkalemia may be increased with concomitant use of β blockers, heparin, low-molecular-weight heparin (LMWH), trimethoprim, amiloride, spironolactone, and salt substitutes, and in patients with diabetes or renal failure. Orthostatic hypotension is common when initiating ACEI therapy, especially in patients who are in a high-renin state, such as patients who are salt or volume depleted (e.g., patients with heart failure, cirrhosis, or diabetes, or receiving diuretics). Patients with bilateral renal artery stenosis, with unilateral stenosis of a solitary functioning kidney, or in a high-renin state (especially patients with heart failure) are susceptible to developing ACEI-induced acute renal failure. Proteinuria, defined as total urinary



• **Fig. 22.1** Angiotensin II formation and actions. ACE, Angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; AT₁, angiotensin II type 1; CAGE, chymostatin-sensitive angiotensin II-generating enzyme.

TABLE 22.4 Pharmacokinetics and Dosage Guidelines for Angiotensin-Converting Enzyme Inhibitors

ACEI Generic Name (Brand Name)	Active Metabolite	Elimination Total	Half-Life of Parent Drug (hr)*	Duration of Action (hr)	Dosage Range (mg/day)	Daily Frequency	Effect of Food on Absorption
Benazepril (Lotensin)	Benazeprilat	11%–12% bile	22	24+	5–80	1	Slightly reduced
Captopril (Capoten)	None	95% urine	2	6–10	12.5–450	2–3	Reduced by 30%–40%
Enalapril (Vasotec)	Enalaprilat	94% urine and feces	11	24	2.5–40	1–2	None
Enalaprilat (Vasotec IV)	None	>90% urine	35		1.25–5	Every 6 hr	NA
Fosinopril (Monopril)	Fosinoprilat	50% urine, 50% feces	12–15	24	10–80	1	Slightly reduced
Lisinopril (Prinivil; Zestril)	None	29% urine, 69% feces, 2% unchanged	13	24	10–40	1	None
Moexipril (Univasc)	Moexiprilat	13% urine, 53% feces	2–9	24	7.5–30	1–2	Markedly reduced
Quinapril (Accupril)	Quinaprilat	60% urine, 37% feces	2–3	24+	20–80	1–2	Reduced
Perindopril (Aceon)	Perindoprilat	96%–78% bile, 4%–12% urine	0.8–1	24	4–16	1	Reduced
Ramipril (Altace)	Ramiprilat	60% urine, 40% feces	11–17	24+	2.5–20	1–2	Slightly reduced
Trandolapril (Mavik)	Trandolaprilat	33% urine, 66% feces	24	24+	1–8	1	Reduced

*Assuming normal renal function.
NA, Not applicable.

protein exceeding 1 g/day and, rarely, accompanied by increases in blood urea nitrogen (BUN) and serum creatinine, may develop in patients receiving high-dose ACEIs or with average ACEI doses and preexisting renal dysfunction. ACEI-induced blood dyscrasias such as neutropenia and agranulocytopenia occur with an incidence of less than 1% and are more common in patients with connective tissue diseases (e.g., systemic lupus erythematosus). ACEIs should be avoided in women of childbearing age because of the potential for fetal and neonatal morbidity and mortality in the second and third trimesters of pregnancy manifesting as skull hypoplasia, hypotension, anuria, and death (pregnancy category D).

Angioedema is rare, occurring in about 1 to 5 of 1000 patients, but it can be life threatening when accompanied by dyspnea. Angioedema can occur at any time during ACEI therapy, especially when starting and stopping regimens. Angioedema generally manifests in the upper extremities, primarily the face, lips, tongue, glottis, and larynx. ACEI-induced angioedema is an absolute contraindication for the administration of alternative ACEIs and a relative contraindication for ARBs, especially in patients with a history of angioedema with dyspnea or with documented aminopeptidase P deficiency. Angioedema symptoms may be associated with high concentrations of bradykinin. Bradykinin exerts its pharmacologic effects (vasodilation and proinflammation) on bradykinin-2 receptors and is metabolized primarily by ACE, to

a lesser extent by aminopeptidase P, and to a minor extent by carboxypeptidase N. Delineating which patients have an aminopeptidase P plasma level deficiency may help predict which patients are predisposed to angioedema.

A significant drug interaction occurs when combining ACEIs with NSAIDs. NSAIDs increase renin release by inhibiting renal vasodilating prostaglandins (PGE₂ and PGI₂), therefore blunting or negating the antihypertensive effects of ACEIs. NSAIDs less likely to reduce renal prostaglandins and to minimize or circumvent the interaction with ACEIs are sulindac (Clinoril), nabumetone (Relafen), etodolac (Lodine), salsalate (Disalcid), and choline magnesium trisalicylate (Trilisate). ACEIs may increase lithium concentrations and have been associated with life-threatening lithium toxicity. ACEI-induced renal sodium depletion may increase lithium renal tubule reabsorption. Patients receiving this combination should be monitored for symptoms of lithium toxicity such as nausea, vomiting, diarrhea, tremor, and mental status changes. Lithium levels should be monitored before and after initiating the ACEI. A quinapril tablet, in contrast to other ACEIs, contains magnesium carbonate at sufficient concentration to reduce tetracycline absorption by 40%. The mechanism of this interaction may be chelation and plausibly may occur with quinolones. To circumvent this interaction, quinapril administration should be spaced 2 to 6 hours apart from tetracycline and quinolone antimicrobials.

Angiotensin II Receptor Blockers

Several nonrenin and non-ACE pathways are used for the production of angiotensin II (see Fig. 22.1). Nonrenin pathways generate angiotensin II from angiotensinogen via tissue plasminogen activator, cathepsin G, and tonin. Non-ACE enzymes that generate angiotensin II from angiotensin I are cathepsin G, chymostatin-sensitive angiotensin II-generating enzyme, and chymase. ACEIs incompletely block the synthesis of angiotensin II. ARBs are angiotensin II type 1 (AT₁) receptor antagonists. AT₁ receptors are found in many tissues, such as adrenal glands (cortex and medulla); vascular smooth muscle; and brain, kidney, liver, uterus, and myocardial tissue. Many tissues also have an angiotensin II type 2 (AT₂) receptor; however, it is not known to have effects on myocardial hemostasis. ARBs have 1000-fold greater affinity for AT₁ receptors than AT₂ receptors and generally do not block the AT₂ receptor. Because ARBs do not inhibit ACE, they do not interfere with the concentrations of bradykinins and substance P. This kinin-sparing effect may explain why ARBs have a low incidence of inducing cough or angioedema. However, the beneficial effects of kinins, including blood pressure and afterload-lowering potency, may be sacrificed.

Eight ARBs are available in the United States. ARBs are indicated for hypertension and can be used to treat heart failure. ARBs have been shown to reduce morbidity, such as target organ damage (e.g., nephropathy) in patients with hypertension, cardiovascular events in patients with systolic heart failure, and progression of nephropathy in patients with type 2 diabetes. In Black patients, ARBs and ACEIs may be less potent antihypertensives; however, this can be circumvented by administering maximal doses.

Compared with ACEIs, ARBs are considered as potent or slightly weaker antihypertensive agents. The inhibition of bradykinin by ACEIs may account for its augmented antihypertensive effect. Angiotensin II receptor blockers arguably are considered second-line agents to ACEIs for hypertension and heart failure and are indicated when ACEI-induced cough or other adverse effects are intolerable. Both ACEIs and ARBs are considered first-line agents for hypertension in nonBlack patients and in patients with CKD, regardless of race. ACEIs or ARBs are considered beneficial

in patients with diabetes and hypertension to prevent progression of renal impairment.⁹ However, ARBs may be considered superior to ACEIs in patients with type 2 diabetic nephropathy. ARBs are administered once or twice daily. Using the combination of an ACEI and an ARB is not recommended due to higher risks of nephrotoxicity. Table 22.5 presents the pharmacokinetics and dosage guidelines for ARBs.^{7,10,11}

The side effect profile of ARBs seems to be similar to that of ACEIs. ARBs may cause orthostatic hypotension, hyperkalemia, neutropenia, nephrotoxicity, and fetotoxicity. Similar warnings and precautions exhibited with ACEIs should be undertaken for ARBs. ARBs can cause cough; however, the incidence is significantly less than with ACEIs. ARBs cause significantly less angioedema than ACEIs; cross-reactivity has been reported. ARBs are not absolutely contraindicated in ACEI-induced angioedema; however, their use in this setting can be dangerous and should be avoided. Rash and dysgeusia are rarely reported with ARBs.

Losartan is extensively metabolized by the hepatic cytochrome P450 (CYP) 3A4 and CYP2C9 isoenzymes to an active carboxylic acid metabolite that is predominantly responsible for the AT₁ blockade and antihypertensive effects of losartan. Drugs that induce these enzyme systems (e.g., phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, and rifabutin) may increase the antihypertensive effects of losartan by increasing the concentration of the active metabolite. Phenobarbital has been shown to decrease the levels of losartan and its metabolite by 20%. Conversely, drugs that inhibit CYP3A4 (e.g., ketoconazole, fluconazole, erythromycin, clarithromycin, fluoxetine, and amiodarone) or CYP2C9 (e.g., amiodarone, cimetidine, and fluoxetine) or CYP3A4 and CYP2C9 simultaneously (e.g., fluoxetine, amiodarone) may decrease the antihypertensive effects of losartan by decreasing the concentration of the active metabolite. However, a study evaluating the effects of cimetidine (CYP3A4 and CYP2C9 inhibitor) on losartan did not yield any changes in the disposition of losartan's carboxylic acid metabolite.

Telmisartan has been shown to increase digoxin peak plasma concentrations by 50%. Digoxin serum concentrations should be monitored before and after the addition of telmisartan. Several mechanistically similar drug-drug interactions that occur with

TABLE 22.5 Pharmacokinetics and Dosage Guidelines for Angiotensin II Receptor Blockers

ARB Generic Name (Brand Name)	Elimination	Terminal Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency	Effect of Food on Absorption
Azilsartan (Edarbi)	55% in feces and 42% in urine	11	40–80	1	No effect
Candesartan (Atacand)	Ester hydrolysis/O-deethylation	9	8–32	1–2	No effect
Eprosartan (Teveten)	80% unchanged, 20% acyl glucuronide	5–9	400–800	1–2	No effect
Irbesartan (Avapro)	CYP2C9, CYP3A4	11–15	150–300	1	No effect
Losartan (Cozaar)	CYP2C9, CYP3A4	2	25–100	1–2	Slightly reduced
Olmesartan (Benicar)	35%–50% in urine and remainder in feces	13	20–40	1	No effect
Telmisartan (Micardis)	Conjugation to acyl glucuronide	24	20–80	1	Slightly reduced
Valsartan (Diovan)	Biliary metabolism	6	80–320	1	Markedly reduced

CYP, Cytochrome P450.

ACEIs are likely to occur with ARBs, such as with NSAIDs and lithium.

Direct Renin Inhibitors

DRIIs act by inhibiting renin, the enzyme that is the first step of the RAAS (see Fig. 22.1). Renin is responsible for the conversion of angiotensinogen to angiotensin I, which is the rate-limiting step in RAAS. Renin inhibition also leads to decreased formation of angiotensin II and aldosterone. However, all agents that inhibit the RAAS, such as ACEIs, have the potential to inhibit feedback inhibition of renin, leading to increases in renin and its activity. This effect can be blocked with the use of a renin inhibitor. DRIIs can be used alone or in combination with other antihypertensive agents.

Aliskiren (Tekturna) is currently the only DRI available on the market. It is indicated only for the treatment of hypertension. Similar to ACEIs and ARBs, aliskiren is considered a poor antihypertensive agent for Black patients. In addition, no studies show that aliskiren is effective in reducing cardiovascular risk. It can be used in combination with any other antihypertensive agents, but it has been studied most comprehensively in combination with ARBs and diuretics.

The most common side effects observed with aliskiren include diarrhea, headache, dizziness, fatigue, upper respiratory tract infection, nasopharyngitis, and back pain. Aliskiren can also cause dry cough, but its incidence is much less than that reported with ACEIs. Similar to other agents that affect the RAAS, aliskiren has been associated with angioedema and has occurred in patients with and without a history of angioedema with ACEI or ARB therapy. Aliskiren possibly may be fetotoxic and is not recommended for use in pregnant patients (pregnancy category D). Rare side effects include increased uric acid levels, renal stones, anemia, rash, renal impairment, myositis, and rhabdomyolysis. Aliskiren monotherapy has a low incidence of hyperkalemia; however, hyperkalemia occurs more frequently when aliskiren is used in combination with ACEIs. It should be used cautiously in combination with other agents that cause hyperkalemia, such as potassium-sparing diuretics and sulfamethoxazole-trimethoprim (Bactrim). Aliskiren is contraindicated in diabetic patients using an ACEI or ARB.

Aliskiren is administered once daily at a dose of 150 to 300 mg. It has very poor oral bioavailability; only about 2.5% is absorbed. Absorption of aliskiren is substantially decreased by high-fat meals; patients should always take it the same way: either with or without food. It undergoes minimal hepatic metabolism by CYP3A4. Cyclosporine and itraconazole, which are potent inhibitors of CYP3A4, were shown to increase aliskiren levels significantly and should not be used concomitantly. Other CYP3A4 inhibitors were also shown to increase aliskiren levels, but the clinical significance of their interaction is unknown. Aliskiren has also been shown to reduce the effectiveness of furosemide by 30% to 50%. The effectiveness of furosemide should be monitored when these two agents are used concomitantly. Approximately 25% of the absorbed dose is excreted unchanged in the urine. Most of the unabsorbed drug is excreted in the feces. No dosage adjustments are recommended at this time in patients with renal or hepatic impairment.^{10–12}

Calcium Channel Blockers

Vascular smooth muscle and cardiac cell contraction depends on free intracellular calcium ion concentration. Calcium enters

vascular smooth muscle cells, myocardial cells, and pacemaker cells through voltage-gated L-type and T-type calcium channels. L-channel blockade mediates coronary and peripheral vasodilation and may cause reflex sympathetic activation or a negative inotropic effect. T-channel blockade also mediates coronary and peripheral vasodilation but is devoid of a reflex sympathetic activation. The influx of calcium from extracellular fluid into cells triggers a second messenger, *inositol triphosphate*, to release stored intracellular calcium from the sarcoplasmic reticulum. This increase in cytosolic calcium results in enhanced binding to the protein *calmodulin*. A calcium-calmodulin complex activates myosin kinase, promoting the interaction between actin and myosin, culminating in cellular contraction. Conventional CCBs inhibit only L-channels. The pharmacodynamic effects of the calcium antagonists on smooth muscle, myocardium, or specialized conduction and pacemaker tissues differ among the agents because of different receptor distribution and densities and the drug's inherent receptor selectivity and affinity.

Nondihydropyridine CCBs include verapamil and diltiazem. Verapamil and, to a lesser extent, diltiazem possess negative **chronotropic** effects by lowering sinoatrial (SA) node automaticity and decreasing atrioventricular (AV) node conduction; these agents are indicated for the treatment of angina and arrhythmias in addition to hypertension. Verapamil and, to a lesser extent, diltiazem are also potent negative **inotropes** and may exacerbate heart failure and should be avoided in patients with severe left ventricular dysfunction.

Dihydropyridine CCBs are potent vasodilators; these agents include amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine. With the exception of nifedipine, dihydropyridine CCBs have negligible chronotropic effects. Immediate-release nifedipine, especially when administered as a liquid, causes a potent reflex tachycardia that increases coronary oxygen demand and has been implicated with an increased risk of MI and stroke. Only sustained-release dosage forms of nifedipine are indicated for hypertension.¹¹ Amlodipine and, plausibly, felodipine may be used in patients with heart failure because these agents do not decrease cardiac contractility. CCBs are very effective antihypertensive agents in both elderly and Black patients. Table 22.6 presents the pharmacokinetics and dose guidelines for calcium antagonists.^{7,11}

Verapamil (e.g., Covera-HS, Verelan PM) and diltiazem (Cardizem LA) have long-acting formulations that are specifically designed to target the **circadian rhythm** of blood pressure throughout the day. Many hypertensive patients have a catecholamine surge with a blood pressure peak in the morning between 6 AM and 12 PM, followed by sustained high (but lower than the peak) blood pressures throughout the day and a nadir at night. Most MIs, strokes, dysrhythmias, and venous thromboembolic events occur in the morning hours, in concert with the circadian blood pressure peaks. CCB formulations are generally designed to be administered at bedtime and begin to release medication in the early morning to achieve a peak effect in the morning hours and a sustained effect during the day.

These novel circadian dosage forms may have limited utility in hypertensive patients who do not have a nadir in blood pressure in the nighttime, or “nondippers.” These formulations leave patients unprotected with a high risk of a coronary event and have not been shown to have better effects on morbidity compared with thiazides and β blockers. Typical hypertensive nondippers (no nighttime nadir) are elderly patients, patients with renal insufficiency, and patients with secondary hypertension. Both verapamil and diltiazem are available in several immediate, extended, and

TABLE 22.6 Pharmacokinetics and Dosage Guidelines for Calcium Channel Blockers

Calcium Antagonist Generic Name (Brand Name)	Onset of Action of Oral Dose Forms (hr)	Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency
Nondihydropyridines				
Verapamil (Calan, Isoptin)	0.5	3–7	180–480	3–4
Verapamil SR (Calan SR, Isoptin SR)	0.5	3–7	120–480	1–2
Verapamil ER (Covera-HS)	4–5	2.8–7.4	180–420	Once at bedtime
Verapamil chronotherapeutic oral drug absorption (Verelan PM)	4–5	3–7	100–400	Once at bedtime
Diltiazem (Cardizem)	0.5	3.5	90–360	3–4
Diltiazem ER capsules (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	1	5	90–540	1–2
Diltiazem ER tablets (Cardizem LA)	3–4	6–9	120–540	Once daily (morning or evening)
Dihydropyridines				
Amlodipine (Norvasc)	6–12	30–50	2.5–10	1
Felodipine (Plendil)	2–5	11–16	5–20	1
Isradipine (DynaCirc)	2	8	2.5–10	2
Isradipine CR (DynaCirc CR)	2	8	2.5–10	1
Nicardipine (Cardene)	20 min	2–4	60–120	3
Nicardipine SR (Cardene SR)	20 min	2–4	60–120	2
Nifedipine (Adalat, Procardia)*	20 min	2–5	30–120	3–4
Nifedipine LA (Adalat CC, Procardia XL)	20 min	7	30–120	1
Nimodipine (Nimotop)†	ND	1–2	360	Every 4 hr for 21 days
Nisoldipine (Sular)	ND	7–12	20–60	1

*Nifedipine (prompt release) is not indicated for hypertension.
†Indicated for subarachnoid hemorrhage, not hypertension.
CC, Coat core; CD, controlled delivery; CR, controlled release; ER, extended release; HS, half strength; LA, long acting; SR, sustained release; XL, XR, extended release; XT, extended technology.

sustained release products. The different dosage formulations of the same drug, with or without circadian effects, are usually not interchangeable and should not be switched on a milligram-to-milligram basis.

The incidence of verapamil-induced and, to a lesser extent, diltiazem-induced constipation is high and often necessitates the use of a stimulant laxative such as bisacodyl or sennosides. Dihydropyridines have potent peripheral vasodilating effects, and they have a high incidence of palpitations, orthostatic hypotension, flushing, headaches, lightheadedness, and syncope. These adverse effects are minimized with long-acting agents. All CCBs may cause peripheral edema, gingival hyperplasia, and gastroesophageal reflux (except diltiazem). CCB-induced peripheral edema does not respond to diuretic therapy and requires discontinuation of the offending agent.

Diltiazem and verapamil inhibit CYP3A4 metabolism and, plausibly, the P-glycoprotein (P-gp) transport of alfentanil, buspirone, carbamazepine, cyclosporine, digoxin, lovastatin, methylprednisolone, quinidine, simvastatin, and tacrolimus, resulting in higher serum levels and potential toxicity. Verapamil and diltiazem

inhibit the hepatic metabolism of theophylline. Although dihydropyridine CCBs are not inhibitors of CYP3A4, they are major substrates of CYP3A4 and may result in significant drug and food interactions through competitive inhibition (metabolism?). Grapefruit juice inhibits the CYP3A4 in the gut and may increase significantly the levels of felodipine, nifedipine, and nisoldipine. Because many CCBs are significantly metabolized by the CYP system, CYP enzyme inducers, such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and rifampin, may lower the serum concentrations of CCBs and compromise efficacy.

β Blockers

The antihypertensive effects of β blockers have multiple mechanisms of action and are as follows:

- Blockade of the β receptors on the renal juxtaglomerular cells, leading to renin blockade and decreased angiotensin II concentrations
- Blockade of myocardial β receptors, leading to decreased cardiac contractility and heart rate, diminishing cardiac output

- Blockade of central nervous system (CNS) β receptors, leading to decreased sympathetic output from the CNS and plausibly blockade of peripheral β receptors, decreasing norepinephrine concentrations

β Blockers cannot be used interchangeably with each other. Instead, disease state guidelines dictate which β blockers to use for each comorbidity. β Blockers with **intrinsic sympathomimetic activity (ISA)**, including acebutolol, carteolol, penbutolol, and pindolol, cause less reduction of resting heart rate, cardiac output, and peripheral blood flow. ISA may be beneficial in patients with stable angina, bradyarrhythmias, compromised pulmonary function, and peripheral vascular (arterial) disease. Labetalol is an α and β blocker with weak β_2 ISA; nevertheless, it is relatively contraindicated in patients with asthma and chronic obstructive pulmonary disease. Labetalol is indicated for hypertension and is often used to manage hypertensive urgencies (oral formulation) and hypertensive emergencies (parenteral formulation). The α and β blocker carvedilol is indicated for patients with hypertension and for patients with mild to moderate heart failure.

Nebivolol (Bystolic) is a highly cardioselective third-generation β_1 blocker that also exhibits vasodilatory properties mediated through nitric oxide, resulting in decreased peripheral vascular resistance, increased stroke volume, and preserved cardiac output. It is approximately three times more β_1 -selective than bisoprolol. It is indicated for the treatment of hypertension and has similar blood pressure reduction effects as atenolol, bisoprolol, ACEIs, ARBs, and CCBs.

β Blockers are indicated for hypertension, angina pectoris, cardiac dysrhythmias, secondary prevention of MI, chronic heart

failure, and pheochromocytoma. β Blockers are no longer considered first-line agents in treatment of essential hypertension but should be reserved as add-on therapy to other antihypertensive agents. β Blockers are also used for migraine prophylaxis, hypertrophic subaortic stenosis, tremors, alcohol withdrawal syndrome, prophylaxis of esophageal variceal rebleeding, anxiety, symptoms of thyrotoxicosis, and in combination with α blockers for pheochromocytoma. Table 22.7 presents the pharmacokinetics and dose guidelines for β blockers.^{7–10}

β Blockers increase triglycerides and decrease high-density lipoproteins; however, this deleterious effect may diminish after prolonged therapy (1 year). β Blockers may cause hyperglycemia and glucose intolerance. These agents can be especially dangerous in diabetics because they mask some of the common symptoms of hypoglycemia, such as palpitations, tremors, and hunger. The use of β blockers in patients with hyperlipidemia or diabetes is acceptable if the lipid and glucose profiles are closely monitored. α and β Blockers and agents with ISA are less likely to affect the lipid and glucose profiles adversely.

β Blocker-induced pulmonary dysfunction may manifest as bronchospasm, bronchial obstruction, wheezing, dyspnea, cough, and exacerbation of previously stable asthma or chronic airway obstruction. Agents with β_1 selectivity, such as atenolol and metoprolol, are less likely to cause pulmonary dysfunction; however, they lose their selectivity with increasing doses. β -Blocking agents may exacerbate intermittent claudication and Raynaud phenomenon, and they may cause CNS disturbances, such as vertigo, tiredness, fatigue, somnolence, mental depression, and nightmares. A correlation between the individual lipid solubility of a β blocker and its ability to penetrate the blood–brain barrier and cause CNS

TABLE 22.7 Pharmacokinetics and Dosage Guidelines for β Blockers

β Blocker Generic Name (Brand Name)	α Blockade	β_1 Selectivity	ISA	Lipid Solubility	Half-Life (hr)	Dosage Range (mg)	Daily Frequency
Acebutolol (Sectral)	0	+	+	Low	3–4	200–200	2
Atenolol (Tenormin)	0	+	0	Low	6–9	25–100	1
Betaxolol (Kerlone)	0	+	0	Low	14–24	5–20	1
Bisoprolol (Zebeta)	0	++	+	Low	9–12	25–200	1
Carteolol (Cartrol)	0	0	+	Low	6	2.5–10	1
Carvedilol (Coreg)	+	0	0	High	7–10	6.25–50	2
Labetalol (Trandate, Normodyne)	+	0	0	Moderate	3–5	100–2400	2
Metoprolol (Lopressor)	0	+	0	Moderate	3–5	50–200	1–2
Metoprolol ER (Toprol-XL)	0	+	0	Moderate	3–7	25–200	1
Nadolol (Corgard)	0	0	0	Low	14–24	20–240	1
Nebivolol (Bystolic)	0	+++	?	Low	11–30	5–40	1
Pindolol (Visken)	0	0	+++	Moderate	3–4	10–60	2
Propranolol (Inderal)	0	0	0	High	4–6	40–240	2
Propranolol LA (Inderal, InnoPran XL)	0	0	0	High	8–10	80–640	1

ER, Extended release; ISA, intrinsic sympathomimetic activity; LA, long acting; XL, extended release; 0, none; +, ++, +++, equals higher degree.

adverse effects may exist. Consequently, agents with high lipophilicity, such as propranolol and penbutolol, have a high incidence of CNS adverse effects. β Blockers should not be discontinued abruptly because this causes a rebound (pretreatment blood pressure) or overshoot (blood pressure higher than pretreatment) hypertension; the drug should be tapered slowly over 1 to 2 weeks before discontinuing entirely.

Several β blockers, including carvedilol, metoprolol, nebivolol, propranolol, and timolol, are CYP2D6 substrates. Fluoxetine, paroxetine, and sertraline are potent CYP2D6 inhibitors and may significantly increase the effect of the substrate β blocker. Because almost all β blockers are significantly metabolized by the CYP system, CYP enzyme inducers, such as cigarettes and marijuana, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and rifampin, may lower serum concentrations of β blockers and compromise efficacy. Atenolol is almost entirely renally eliminated and may be used as an alternative to β blockers that interact via hepatic mechanisms or in patients with liver disease.

Diuretics

Diuretics are divided into the following five classes:

1. Thiazides and thiazide-like agents
2. Loop diuretics
3. Potassium-sparing agents
4. Carbonic anhydrase inhibitors (CAIs) (e.g., acetazolamide [Diamox])
5. Osmotics (e.g., mannitol)

Thiazides can be used as part of first-line treatment combinations for the management of hypertension in patients without comorbidities.⁴ Thiazides, loop diuretics (except ethacrynic acid), and CAIs are sulfonamide-containing agents and may cross-react in patients who have a history of sulfonamide allergy. Sulfonamide-containing agents include sulfonylurea antidiabetics, silver sulfadiazine, tamsulosin, celecoxib, and probenecid. A significant drug–drug interaction occurs when combining diuretics with NSAIDs and combining sodium-depleting diuretics with lithium. The mechanisms of these interactions are similar to the mechanisms of ACEIs and have been discussed previously in this chapter.

Potassium-Sparing Diuretics

Potassium-sparing agents are weak hypotensive agents when used alone, but they provide an additive hypotensive effect when used in combination with thiazide diuretics. The two agents used clinically are amiloride (Midamor) and triamterene (Dyrenium). These agents are employed primarily for their antidiuretic effects, which offset the potassium excretion effects of other diuretics. These agents work by blocking sodium channels in the luminal membrane of cells in the distal tubule and collecting duct, attenuating the excretion of potassium, calcium, and magnesium. Both hypokalemia and hypomagnesemia have been implicated as a cause of cardiac arrhythmias; there is an advantage to adding these agents to diuretic antihypertensive therapy. The magnesium-sparing effects of potassium-sparing diuretics may be an added benefit compared with a diuretic plus a potassium supplement.

Both potassium-sparing diuretics can cause gastrointestinal side effects, such as dyspepsia, abdominal cramps, nausea, and diarrhea; CNS side effects, such as mental confusion, lethargy, headache, and dizziness; and hematologic, dermatologic, and musculoskeletal (leg cramps) adverse effects. Triamterene has been

associated with interstitial nephritis and nephrolithiasis; the incidence may be 1 in 200. Triamterene is photosensitizing, which may be additive when combined with phototoxic sulfonamide-containing thiazide diuretics. Triamterene may cause hyperuricemia and hyperglycemia.

Thiazide and Thiazide-Like Diuretics

Thiazide diuretics increase sodium and chloride excretion by interfering with their reabsorption in the distal tubule; a mild diuresis of slightly concentrated urine results. Excretion of potassium, bicarbonate, magnesium, phosphate, and iodide is also increased, whereas calcium excretion is decreased. Although thiazides decrease extracellular fluid volume, antihypertensive activity is caused primarily by direct vasodilation. Thiazides are indicated for hypertension, chronic edema, chronic heart failure, and ascites. Thiazides generally take 2 to 4 weeks to elicit their full pharmacologic effect. Thiazides have a **dose-ceiling effect**, at which point the antihypertensive effects do not increase despite dose increases; however, the toxic effects do *not* have a dose-ceiling effect.

Because thiazides cause hypercalcemia, they may be a useful adjunct in the management and prevention of osteoporosis. Although chlorthalidone, indapamide, and metolazone do not possess the benzothiadiazine structure, pharmacologically they act like thiazide diuretics—they are thiazide-like in structure and activity. Thiazide diuretics lose their antihypertensive potency in patients with a **creatinine clearance (CrCl)** less than 30 mL/min. Indapamide retains its potency, however, in patients with a CrCl greater than 15 mL/min. Metolazone is the only thiazide-like diuretic that retains potency in patients with a CrCl less than 15 mL/min. Despite the thiazide-like structure of metolazone, its pharmacologic effects are similar to those of loop diuretics. Metolazone is often added to a loop diuretic in patients with diuretic resistance, achieving a synergistic diuretic effect. Mykrox tablets are a formulation of metolazone with a higher bioavailability than conventional metolazone, resulting in a more rapid diuretic effect; Mykrox is not therapeutically equivalent to Zaroxolyn, but it is no longer available on the market. Table 22.8 presents the pharmacokinetics and dose guidelines for thiazide and thiazide-like diuretics.^{4,7,11}

Common side effects observed with thiazide and thiazide-like diuretics include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, hyperlipidemia, and sexual dysfunction. These abnormalities are dose related and may be minimized by using low-dose agents such as chlorthalidone, 12.5 to 25 mg daily, or hydrochlorothiazide, 25 mg once daily. Less common thiazide-induced adverse effects include dyspepsia, rashes, photosensitivity, thrombocytopenia, and pancreatitis.

Loop Diuretics

Loop diuretics, often referred to as *high-ceiling diuretics*, act principally at the thick ascending limb of the loop of Henle, where they decrease sodium reabsorption by competing for the chloride site on the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ symporter (a transport molecule). Excretion of sodium, chloride, potassium, hydrogen ion, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is enhanced. Diuretics such as thiazides have a limited diuretic potency with a plateau effect because they act primarily at sites past the ascending limb; only a small percentage of the filtered load reaches these more distal sites. Because more than 25% of the filtered load is reabsorbed in the ascending limb, loop diuretics are highly efficacious with increasing doses, and this is why they are termed high-ceiling diuretics.

TABLE 22.8 Pharmacokinetics and Dosage Guidelines for Thiazides and Thiazide-Like Diuretics

Thiazide/Thiazide-Like Diuretic Generic Name (Brand Name)	Bioavailability	Peak Effect (hr)	Duration of Diuresis (hr)	Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency
Chlorothiazide (Diuril)	10–20	2 (PO), 0.5 (IV)	6–12 (PO), 2 (IV)	1–2	500–2000	1–2
Chlorthalidone (Hygroton)	65	2	24–72	35–55	15–200	1
Hydrochlorothiazide (Esidrix, HydroDIURIL, Oretic, Microzide)	65–75	4–6	6–12	2.5–4.5	25–100	1–2
Indapamide (Lozol)	95	2	24–36	14–18	1.25–2.5	1
Metolazone (Zaroxolyn)	65	2	12–24	6–20	5–20	1
Metolazone (Mykrox)		2–4	12–24	14	0.5–1	1

IV, Administered intravenously; PO, administered orally.

TABLE 22.9 Pharmacokinetics and Dosage Guidelines for Oral Loop Diuretics

Loop Diuretic Generic Name (Brand Name)	Bioavailability (%)	Onset (hr)	Duration (hr)	Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency
Bumetanide (Bumex)	70–95	0.5–1	5–6	0.8 ± 0.2	0.5–10	1
Ethacrynic acid (Edecrin)	100	0.5	6–8	2–4	50–200	1–2
Furosemide (Lasix)	60	0.5–1	6–8	0.5–1.1	40–240	1–2
Torsemide (Demadex)	80	0.5–1	1	2–4	5–200	1

Loop diuretics are indicated for chronic heart failure, ascites with or without hepatic cirrhosis, renal failure, pulmonary edema, hypercalcemia, hypermagnesemia, and syndrome of inappropriate antidiuretic hormone. Loop diuretics are second-line diuretics in the management of hypertension; however, they are superior to thiazide diuretics in diuresis and decreasing blood pressure for patients with renal insufficiency. [Table 22.9](#) presents the pharmacokinetics and dose guidelines for oral loop diuretics.^{4,7,11}

Loop diuretics are very potent and consequently may cause severe dehydration, hypotension, hypochloremic alkalosis, and hypokalemia. Loop diuretics should not be administered at bedtime because the patient will have to urinate frequently, causing sleep disturbances. Loop diuretics may cause hyperglycemia (not reported with bumetanide), hyperuricemia, dyspepsia, photosensitivity, and ototoxicity. Ethacrynic acid is the most auditory ototoxic loop diuretic and should be considered only for patients refractory to other loop diuretics or when there is a history of a life-threatening sulfonamide allergy.

Aldosterone Antagonists

Spironolactone (Aldactone) and eplerenone (Inspra) are aldosterone antagonists that exert their effect on the late distal tubule and collecting duct. Spironolactone, a weak diuretic, is used primarily for its aldosterone antagonist effects. Spironolactone is indicated for hypertension, management of hepatic cirrhosis (diuretic of choice), primary hyperaldosteronism, hypokalemia, and heart

failure. For hypertension, spironolactone is used in combination with other antihypertensives or to spare potassium when administered with diuretics. The chemical structure of spironolactone resembles the structure of the corticosteroids and may explain its sexual adverse effects, such as impotence, decreased libido, gynecomastia, deepening of the voice, menstrual irregularities, and hirsutism. Other spironolactone-induced adverse effects include diarrhea, gastritis, skin rashes, drowsiness, lethargy, ataxia, headaches, and confusion. Similar to the other potassium-sparing diuretics, spironolactone may cause hyperkalemia. [Table 22.10](#) presents the pharmacokinetics and dosage guidelines for the aldosterone antagonists.^{4,7,11}

Eplerenone is indicated for heart failure after MI and hypertension. Similar to spironolactone, eplerenone blocks the mineralocorticoid receptor, but, in contrast to spironolactone, it does not block the progesterone or androgen receptor, minimizing the sexual adverse effects such as gynecomastia, breast pain, impotence, and menstrual irregularities. Eplerenone has a higher incidence of severe hyperkalemia, especially in patients with reduced renal function. Because of the risk of severe hyperkalemia, eplerenone is contraindicated in all patients with potassium values greater than 5.5 mEq/L or CrCl less than 30 mL/min and in hypertensive patients with type 2 diabetes and microalbuminemia, concomitant use of potassium supplements or potassium-sparing diuretics, or serum creatinine greater than 2 mg/dL in men and greater than 1.8 mg/dL in women or a CrCl less than 50 mL/min. Vigilant monitoring of serum potassium levels is necessary when eplerenone is administered with ACEIs, ARBs, or

TABLE 22.10 Pharmacokinetics and Dosage Guidelines for Aldosterone Antagonists

Aldosterone Antagonist	Active Metabolite	Elimination Total	Onset of Action (hr)	Peak Response	Duration of Action (hr)	Half-Life of Parent Drug (hr)	Dosage Range (mg/day)	Daily Frequency	Effect of Food on Absorption
Spironolactone (Aldactone)	Canrenone	47%–57% renal, 35%–41% fecal	2–4	6–8 hours	16–24	1.4	25–400	1–2	Increased
Eplerenone (Inspra)	None	67% renal, 32% fecal	1–2	4 weeks	24	3.5–6	50–100	1–2	No effect

TABLE 22.11 Pharmacokinetics and Dosage Guidelines for Centrally Acting Adrenergic Agents (α_2 Agonists)

α_2 Agonist Generic Name (Brand Name)	Onset of Action (hr)	Peak Effect (hr)	Duration of Action (hr)	Half-Life (hr)	Elimination	Dosage Range (mg/day)	Daily Frequency
Methyldopa (Aldomet)	4–6	6–9	24–48	1.25	Renal (biphasic)	500–2000	2–3
Clonidine (Catapres)	0.5–1	3–5	24	6–20	Renal (40%–60%)	0.1–2.4	2–4
Guanfacine (Tenex)	2.5	6	24	17	Renal (50%)	1–3	Once at bedtime
Guanabenz (Wytensin)	1	2–5	6–8	7–10	Renal (70%–80%)	4–32	2

β blockers. Eplerenone is a CYP3A4 substrate; CYP3A4 inhibitors such as verapamil, diltiazem, erythromycin, fluconazole, and saquinavir may increase eplerenone levels by 50%. It is recommended to avoid eplerenone in patients who are taking strong CYP3A4 inhibitors.

Centrally Acting Adrenergic Agents

The centrally acting adrenergic agents, or α_2 agonists, decrease blood pressure by affecting cardiac output and peripheral resistance; they are negative inotropes and chronotropes. α_2 Agonists stimulate brainstem α_2 receptors, resulting in a decrease in sympathetic outflow from the CNS. α_2 Agonists are very effective antihypertensives; however, they are not considered first-line therapy because of their side effect profile. They have a high incidence of anticholinergic-like side effects, such as sedation, blurred vision, dry mouth, constipation, and urinary retention; and CNS side effects, such as drowsiness, fatigue, headaches, depression, psychosis, and nightmares. Long-term use of these agents results in sodium and fluid retention and almost always necessitates the use of concomitant diuretics; this is especially seen with methyldopa. α_2 Agonists are not recommended for noncompliant patients and should never be withdrawn abruptly because of the risk of either rebound hypertension or overshoot hypertension.

The most effective and least toxic α_2 agonist is the clonidine transdermal therapeutic system (Catapres-TTS), which achieves sustained levels of clonidine for 7 days. The sustained clonidine levels avoid the peaks and troughs associated with the prompt-release dosage form, and treatment is relatively devoid of the troublesome anticholinergic and CNS side effects. The clonidine patch is applied to a hairless area of intact skin on the upper torso. On the initial application, the clonidine patch takes 2 to 3 days to achieve target blood levels and a therapeutic effect. It is

recommended to co-administer clonidine oral tablets along with the patch for the first 2 to 3 days of therapy. The most common adverse effects of the patch are local skin rashes and irritation. Table 22.11 presents the pharmacokinetics and dosage guidelines for α_2 agonists.^{4,7,11}

α_1 -Adrenergic Antagonists

α_1 -Adrenergic receptor antagonists selectively block postsynaptic α_1 receptors. Total peripheral resistance is reduced through arterial and venous dilation; these agents decrease both preload and afterload and cause a potent first-dose sympathetic reflex increase in heart rate and renin activity.¹³ α_1 -Adrenergic antagonists cause a first-dose phenomenon that manifests with orthostatic hypotension, tachycardia, palpitations, dizziness, headaches, and syncope. After several doses, despite persistent vasodilation, tolerance to the first-dose phenomenon develops, and heart rate, renin, and cardiac output return to normal. To minimize the first-dose phenomenon, initial doses of α_1 -adrenergic antagonists should be low and administered at bedtime.

α_1 -Adrenergic antagonists are indicated for hypertension, benign prostatic hyperplasia (BPH), heart failure, and Raynaud vasospasm; an exception is uroselective α_1 -adrenergic antagonists (tamsulosin and alfuzosin), which are indicated only for BPH. In contrast to other antihypertensives, α_1 -adrenergic antagonists have favorable effects on the lipoprotein profile and may decrease triglycerides and low-density lipoproteins and increase high-density lipoproteins by 5% to 10%, making them an ideal drug of choice. However, the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study compared doxazosin with other antihypertensives (chlorthalidone) and revealed a 25% higher incidence of combined cardiovascular morbidity in patients receiving doxazosin.¹⁴ A higher incidence of doxazosin-induced stroke, heart failure, angina, and coronary

TABLE 22.12 Pharmacokinetics and Dosage Guidelines for α_1 -Adrenergic Receptor Antagonists

α_1 Antagonist Generic Name (Brand Name)	Elimination Routes	Peak Effect (hr)	Duration of Action (hr)	Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency
Doxazosin (Cardura)	63% feces, 9% urine	6	18–36	11	1–16	1
Prazosin (Minipress)	90% feces, 10% urine	1.5	8–10	2	3–40	2–3
Terazosin (Hytrin)	60% feces, 40% urine	2	24	14	1–20	1–2

TABLE 22.13 Pharmacokinetics and Dosage Guidelines for Oral Vasodilators

Vasodilators Generic Name (Brand Name)	Bioavailability (%)	Onset of Action (min)	Terminal Half-Life (hr)	Dosage Range (mg/day)	Daily Frequency
Hydralazine (Apresoline)	30–5	20–30	2–8 ESRD: 7–16	40–300	3–4
Minoxidil (Loniten)	90	30	3.5–4.2	5–100	1

ESRD, End stage renal disease.

revascularization was reported. On the basis of the results of this study, α_1 -adrenergic antagonists are considered second-line antihypertensive therapy. Table 22.12 presents the pharmacokinetics and dosage guidelines for α_1 -adrenergic antagonists.^{4,7,11}

Antiadrenergic Agents

Reserpine is an antiadrenergic antihypertensive agent and is a second-line antihypertensive. Reserpine works by binding to storage vesicles of peripheral and central postganglionic adrenergic neurons and depleting norepinephrine. Subsequently, reserpine renders the neuronal storage vesicles dysfunctional. Reserpine may cause sedation, depression, suicidal ideation, psychosis, peptic ulcer disease, and nasal stuffiness. The side effects of reserpine can be minimized with low yet effective antihypertensive doses (0.25 mg or less). The antihypertensive effects may be diminished when combined with tricyclic antidepressants, amphetamines, and ephedrine.

Vasodilators

The two common vasodilators used in the management of hypertension are hydralazine (Apresoline) and minoxidil (Loniten). Because of their side effect profile, the vasodilators are second-line antihypertensive agents. Hydralazine has also been used for angina and is indicated for heart failure in combination with isosorbide dinitrate. Hydralazine and isosorbide dinitrate are recommended to reduce morbidity and mortality in patients self-identified as African Americans with New York Heart Association (NYHA) class III to IV heart failure with reduced ejection fraction receiving optimal therapy with ACEIs or ARBs and β blockers and in patients with current or prior symptomatic heart failure with reduced ejection fraction who have a contraindication to ACEI or ARB use.^{15–17}

Hydralazine and minoxidil reduce total peripheral resistance by a direct action on vascular smooth muscle, increasing intracellular

concentrations of cyclic guanosine 3',5'-monophosphate (cGMP). These vasodilators are so potent that they cause a profound activation of baroreceptors, leading to reflex tachycardia, renin release, and an increase in cardiac output. To minimize tachycardia and fluid retention, these agents are often administered concomitantly with a β blocker and a loop diuretic, respectively. Hydralazine has been associated with peripheral neuropathy and drug-induced systemic lupus erythematosus-like syndrome. When hydralazine is administered with food, its bioavailability may double and may cause cardiac toxicity. Hydralazine should be administered consistently with or without food. Minoxidil-induced adverse effects include hirsutism, nausea and vomiting, and pericardial effusions.¹⁸ Table 22.13 shows the pharmacokinetics and dosage guidelines for the oral vasodilators.

Angina

Epidemiology, Etiology, and Pathophysiology

KEY POINT

Angina pectoris is a marker for myocardial ischemia.

Ischemic heart disease can manifest as many clinical variants such as stable exertional angina; unstable (rest, preinfarction, crescendo) angina; coronary vasomotion; vasospasm associated with atypical, variant, or Prinzmetal angina; silent myocardial ischemia, or MI. Angina pectoris (chest pain) is a symptom or marker of myocardial ischemia. Ischemia is defined as a lack of oxygen and decreased or no blood flow to the myocardium. From 1998 to 2012, 3.4 million Americans over the age of 40 experienced angina each year.¹⁹ Women often initially present with angina, whereas men present with MI. Coronary artery disease (CAD), when present, tends to be less severe in women than men.

Angina pectoris can manifest with a heavy weight or pressure on the chest, a burning sensation, or shortness of breath. The chest

tightness or pressure can occur over the sternum, left shoulder, and lower jaw. Chest pain can be precipitated by physical exercise, a cold environment, or emotional stress (anger). The duration of pain intensity may range from a few minutes to half an hour. During angina, an imbalance of myocardial oxygen supply and myocardial oxygen demand occurs. Factors that increase myocardial oxygen demand include increased heart rate, increased systolic wall force or tension, or increased contractility. Factors that decrease myocardial oxygen supply include a decrease in the concentration of oxygen (e.g., anemia), a decrease in coronary blood flow (e.g., thrombus), or inability of the myocardium to extract oxygen from the blood.

Pharmacotherapy

KEY POINT

Pharmacotherapy for angina includes nitrates (e.g., nitroglycerin), β blockers, and calcium antagonists.

Pharmacotherapy for angina pectoris includes nitrates, β blockers, CCBs, and ranolazine (Ranexa). Ranolazine was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of chronic stable angina in combination with amlodipine, β blockers, or nitrates.^{20,21} For the management of vasospastic and chronic stable angina, diltiazem, verapamil, amlodipine, and nifedipine are indicated. For the management of angina, β blockers are usually dosed to achieve a resting heart rate of 50 to 60 beats/min and a maximal exercise heart rate of 100 beats/min. All patients with angina should receive daily aspirin (75 to 100 mg/day) to prevent MI.^{20–22}

Nitrates

Nitroglycerin reduces myocardial oxygen demand by causing venodilation of coronary arteries and collaterals, resulting in decreased end-diastolic pressures. Venous effects predominate; however, nitroglycerin can affect arteries at high doses. The cellular mechanism of action of nitrates is depicted in Fig. 22.2. Nitrates are indicated for acute treatment or prophylaxis of angina, acute MI, acute heart failure, low-output syndromes, and hypertension (intravenous). Nitrates may be administered by various routes and are readily available in multiple preparations, including oral, intravenous, ointment, transdermal, translingual, and sublingual tablets. Sublingual nitroglycerin is indicated for acute anginal relief. Sublingual nitroglycerin has an onset of action of minutes and duration of action of 30 minutes. Sublingual nitroglycerin should be administered every 5 minutes up to three doses. If pain relief is not achieved within 3 to 5 minutes after the first dose, emergency care should be sought.²² Sublingual tablets must always be stored in their original glass container, and any unused tablets should be discarded 6 months after the original container is opened because of loss of potency. Other forms of nitroglycerin are isosorbide dinitrate (Isordil) and isosorbide mononitrate (Imdur, Ismo, and

Monoket). Table 22.14 presents the pharmacokinetics and dosage guidelines of nitrates.

Serious adverse reactions to nitrates are uncommon and involve mainly the cardiovascular system. The most frequent adverse effects include tachycardia, palpitations, postural hypotension, dizziness, flushing, and headache. Case reports of clinically significant methemoglobinemia are rare at conventional doses. Methemoglobinemia formation is dose related and occurs by the nitrite ion reacting with the ferrous hemoglobin. Tolerance to the vascular and antianginal effects may occur after 24 hours of continuous therapy with any formulation. Because most evidence supports the central role of cGMP stimulation in nitrate-induced vasodilation, it has been suggested that the tolerance results from sulfhydryl depletion at the nitrate receptor. Sulfhydryl depletion leads to reduced S-nitrosothiol production and a decreased production of cGMP. Theoretically, administration of a sulfhydryl donor, such as N-acetyl cysteine or captopril, may restore vascular response to nitrates. Increasing doses of nitroglycerin overcome tolerance, but this is short lived. To circumvent nitrate tolerance, a nitrate-free interval of 10 to 14 hours is suggested. Nitrates are contraindicated in patients concomitantly taking phosphodiesterase type 5 inhibitors for erectile dysfunction, such as sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), because of pronounced potentiation of nitric oxide resulting in profound hypotension, MI, and even death.

Ranolazine

Ranolazine is indicated for the treatment of patients with chronic angina who have not achieved an adequate response with other antianginal drugs. In 2012 the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) suggested that ranolazine may be safely administered for symptomatic relief, but it does not seem to reduce significantly cardiovascular death, MI, or recurrent ischemia. Ranolazine provides anti-ischemic effects that complement the benefits of CCBs, β blockers, and nitrates. Although the exact mechanism of how ranolazine exerts its antianginal and antiischemic effects is unknown, it may accomplish that by selectively inhibiting the late phase of the inward sodium channel in ischemic myocytes, resulting in decreased myocardial oxygen consumption.^{23,24} Ranolazine increases exercise tolerance, which reduces angina frequency and the need for emergent nitroglycerin interventions. In contrast to standard antianginal medications, ranolazine does not alter blood pressure or heart rate. The initial adult dose of ranolazine extended-release tablets is 500 mg twice daily, with a maximal dose of 1 g twice daily.

Adverse reactions observed with ranolazine include dizziness, palpitations, headache, constipation, nausea, abdominal pain, and peripheral edema. Small, reversible increases in serum creatinine and BUN have also been observed without the incidence of renal toxicity. Ranolazine is excreted primarily in the urine (75%) and, to a lesser extent, in the feces (25%); however, the manufacturer suggests that no dosage adjustments are needed in patients with



• **Fig. 22.2** Mechanism of action of nitrates on smooth muscle relaxation. Nitrates are converted intracellularly (denitration) to nitric oxide and 5-nitrosothiol. Nitric oxide interacts with and activates guanylyl cyclase to increase intracellular concentrations of cyclic guanosine 3',5'-monophosphate (cGMP). Increased cGMP results in phosphorylation of various proteins, which reduces calcium (Ca^{++}) release from the sarcoplasmic reticulum, subsequently causing smooth muscle relaxation.

TABLE 22.14 Pharmacokinetics and Dosage Guidelines for Nitrates

Name	Dosage Forms	Onset of Action (min)	Duration of Action (hr)	Initial Dosage
Nitroglycerin	Buccal tablet, ER Oral capsule, ER Oral tablet, ER Sublingual spray Sublingual tablet Intravenous solution Topical ointment Transdermal patch	Angina pectoris • Oral ER: 20–45 • Sublingual: 1–3 • Topical ointment: 30–60 • Transdermal patch: 30–60 • Translingual spray: 2 • Perioperative hypertension • IV: 1–5	Oral ER: 3–8 Sublingual: up to 1 Topical ointment: 7 Transdermal patch: 8–10 Transdermal spray: up to 1	<i>Angina pectoris</i> • IV: 5–25 mcg/min to response • Oral capsule, ER: 2.5–9 mg every 12 hr; may increase to every 8 hr if needed and if tolerated • Topical ointment: 7.5–30 mg applied twice daily to a 36-square-inch area of truncal skin • Transdermal patch: 0.2–0.4 mg/hr • Sublingual tablet: 0.3–0.6 mg every 5 min, 3 times • Sublingual spray: 1–2 metered sprays onto or under the tongue; may repeat in 3–5 min, with no more than 3 metered sprays in 15 min • Chronic heart failure • IV: non-PVC tubing, 5 mcg/min, initial titration should be in 5-mcg/min increments at intervals of 3–5 min guided by patient response • Perioperative hypertension • IV: 5 mcg/min, initial titration should be in 5-mcg/min increments at intervals of 3–5 min, guided by patient response
Isosorbide dinitrate	Oral capsule, ER Oral tablet Oral tablet, chewable Oral tablet, ER Sublingual tablet	Oral: 60 Oral tablet, chewable: 2–3 Sublingual tablet: 2–10	Oral: 8 Oral tablet, chewable: 2 Sublingual tablet: 1–2	<i>Angina pectoris</i> • Oral tablet (immediate release): 5–20 mg two or three times daily • Oral tablet/capsule, ER: 40 mg once or twice daily • Oral tablet, chewable: 5–10 mg every 2–3 hr or as needed; titrate to effect • Chronic heart failure • Sublingual tablet: 5–15 mg every 2–3 hr • Oral: 30–160 mg/day in divided doses
Isosorbide mononitrate	Oral tablet Oral tablet, ER	45–60	6–12	<i>Angina pectoris</i> • Oral tablet (immediate release): 5–20 mg twice or three times daily • Oral tablet: 20 mg every morning, then 20 mg 7 hr later • Oral tablet, ER: 30–60 mg once daily <i>Myocardial infarction</i> • Oral tablet: 20 mg once to three times daily

ER, Extended release; IV, intravenous; PVC, polyvinyl chloride.

renal impairment. Nevertheless, patients with renal impairment taking ranolazine were observed to have a 15-mm Hg increase in blood pressure—frequent blood pressure monitoring is prudent in such patients. Ranolazine can prolong the cardiac Q–T_c interval (Q–T interval [duration of ventricular electrical activity], corrected for heart rate) and place patients at risk of torsades de pointes; this effect is dose dependent. A dose of 1 g twice daily prolongs the Q–T_c by 6 msec and is more pronounced with hepatic dysfunction. Ranolazine is contraindicated in patients with any degree of hepatic dysfunction or who are receiving other agents that prolong the Q–T_c. Baseline and follow-up electrocardiography (ECG) should be completed during ranolazine therapy.

Ranolazine is extensively metabolized in the gut and liver by CYP3A4 and, to a lesser extent, by CYP2D6. CYP3A4 inhibitors, such as ketoconazole, fluconazole, macrolides, diltiazem, and verapamil, can significantly increase the plasma levels of ranolazine and are contraindicated. Ranolazine is a substrate of P-gp, and it should not be taken with verapamil, a known inhibitor of P-gp.

Ranolazine is a P-gp inhibitor and has been shown to increase the plasma concentration of digoxin by 1.5-fold. Ranolazine is also an inhibitor of CYP3A4 and CYP2D6, plausibly increasing the plasma levels of drugs that are substrates of these enzymes, such as statins, tricyclic antidepressants, and antipsychotics. Dose of simvastatin should be limited to 20 mg per day when taking ranolazine.²⁴

Antithrombotic Agents

KEY POINT

Antithrombotic agents include anticoagulants (e.g., heparin, low-molecular-weight heparin [LMWH], direct thrombin inhibitors [DTIs], factor Xa inhibitors, and coumarins); antiplatelet agents (e.g., aspirin, dipyridamole, cilostazol, pentoxifylline, ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor, glycoprotein [GP] IIb/IIIa inhibitors, and vorapaxar); and thrombolytic agents (i.e., agents that lyse clots, such as streptokinase and alteplase).

• BOX 22.1 List of Antithrombotic Agents

Anticoagulant Agents

Parenteral Anticoagulants

- High-molecular-weight heparin
 - Unfractionated heparin
- Low-molecular-weight heparins
 - Dalteparin (Fragmin)
 - Enoxaparin (Lovenox)
- Selective factor Xa inhibitor
 - Fondaparinux (Arixtra)
- Direct thrombin inhibitors
 - Argatroban
 - Bivalirudin (Angiomax)
 - Desirudin (Iprivasc)
 - Lepirudin (Refludan)

Oral Anticoagulants

- Warfarin sodium (Coumadin)
- Direct thrombin inhibitor
 - Dabigatran (Pradaxa)
- Selective factor Xa inhibitors
 - Apixaban (Eliquis)
 - Rivaroxaban (Xarelto)
 - Edoxaban (Savaysa)
 - Betrixaban (Bevyxxa)

Antiplatelet Agents

- Aspirin
- Clopidogrel (Plavix)
- Prasugrel (Effient)
- Ticagrelor (Brilinta)
- Cangrelor (Kangreal)
- Cilostazol (Pletal)
- Dipyridamole (Persantine)
- Aspirin and extended-release dipyridamole (Aggrenox)
- Ticlopidine HCl (Ticlid)
- Vorapaxar (Zontivity)
- Glycoprotein IIb/IIIa inhibitors
 - Abciximab (ReoPro)
 - Eptifibatide (Integrilin)
 - Tirofiban (Aggrastat)

Thrombolytic Agents

- Alteplase (Activase)
- Reteplase (Retavase)
- Streptokinase (Streptase)
- Tenecteplase (TNKase)

Antithrombotics may be defined as agents that prevent or break up blood clots in conditions such as thrombosis or embolism. Three categories of antithrombotic agents are currently available in the United States: anticoagulants, antiplatelets, and thrombolytics. Anticoagulant agents work by preventing the formation of the fibrin clot and preventing further clot formation in already existing thrombi. Antiplatelet agents inhibit the action of platelets in the initial stage of the clotting process. Thrombolytics break up thrombi by degrading fibrin. [Box 22.1](#) lists currently available antithrombotic agents.²⁵

Formation and Elimination of Acute Coronary Thrombus

Under normal conditions, the body maintains an equilibrium state between clot formation (thrombosis) and clot breakdown

(fibrinolysis).²⁶ Thromboses are initiated by an injury to the endothelial wall of a coronary vessel. When injury occurs, the anticoagulated endothelial surface is disrupted, and the highly procoagulant subendothelial surface is exposed. Instantaneously platelets aggregate in response to the release of chemotactic substances, such as thromboxane A_2 ; this is followed by platelet adhesion to the subendothelial vessel surface, representing the initial step in clot formation. Platelet adhesion is mediated mainly by von Willebrand factor, which is present in the subendothelium and is actively recruited when the subendothelium is injured. Adhered platelets are exposed to many subendothelial proteins, such as collagen and thrombin. Collagen and thrombin also promote platelet activation. Activated platelets release platelet agonists such as adenosine diphosphate (ADP), norepinephrine, serotonin, and arachidonic metabolites, mitigating and amplifying platelet aggregation and forming an unstable thrombus or platelet plug.

The most important consequence of platelet activation is the expression of platelet receptor glycoprotein (GP) IIb/IIIa on the platelet's surface, allowing binding to fibrinogen. Fibrinogen binds to the two GP IIb/IIIa molecules, causing a cross-linking of receptors on adjacent platelets and initiating platelet aggregation. Triggers affecting platelet aggregation and their antagonists are depicted in [Fig. 22.3](#). Fibrinogen is converted into fibrin monomers by the action of thrombin; this is the final step in clot formation. Homeostasis is complete when the fibrin clot becomes insoluble within the vessel. This stable fibrin clot is the end result of the coagulation cascade. Under normal conditions, multiple inhibitors and control mechanisms keep these reactions localized to the site of the injury.

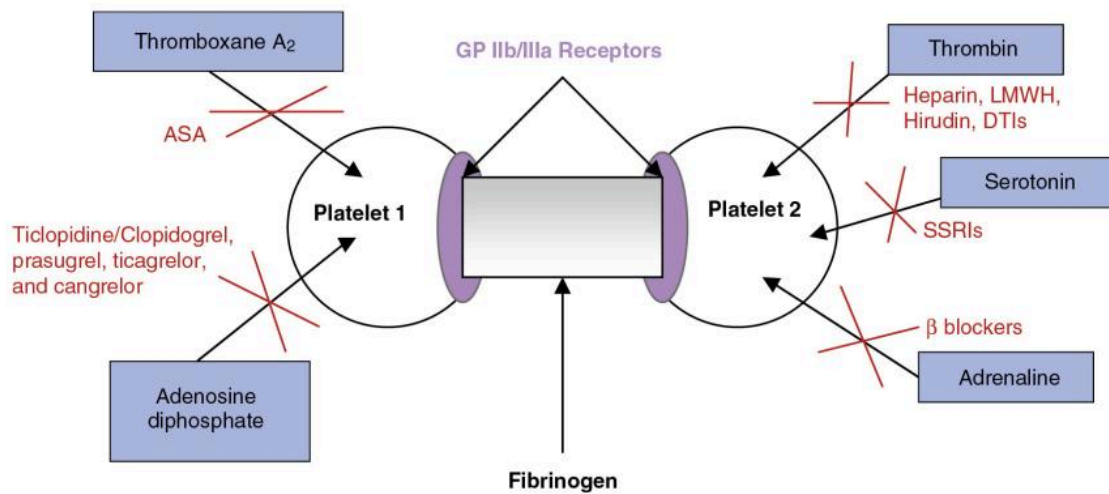
The fibrin clot ultimately must be removed for hemostasis to be maintained. Activation of the fibrinolytic system by tissue plasminogen activators (tPAs), which are present in most body fluids and tissues, results in the conversion of plasminogen to plasmin, initiating the dissolution of fibrin and fibrinogen. The breakdown of fibrinogen and fibrin results in polypeptides termed **fibrin split** or **fibrinogen degradation products (FDPs)**. FDPs are anticoagulant substances that can cause bleeding, if fibrinolysis becomes uncontrolled and excessive. **D-dimers** are fragments of plasmin-digested, cross-linked fibrin that increase in concentration after the onset of fibrinolysis. Blood testing for D-dimer fragments may assist in the diagnosis of pathogenic venous thromboembolism (VTE). The extrinsic and intrinsic pathways of the coagulation system²⁷ are depicted and described in [Fig. 22.4](#).

Anticoagulant Agents

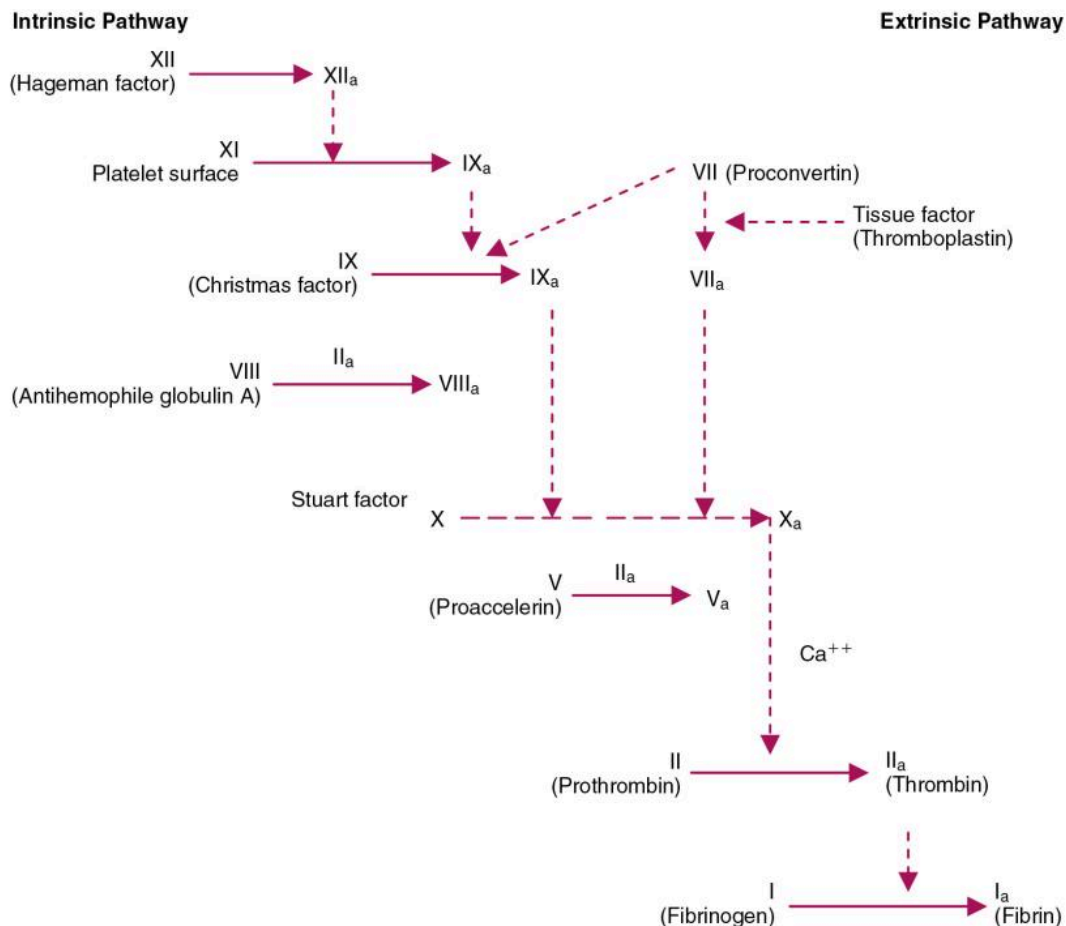
Heparins: Unfractionated Heparin and Low-Molecular-Weight Heparin

Heparin is a nonionic sulfated glycosaminoglycan anticoagulant naturally present in the secretory granules of human mast cells. When heparin is released from mast cells, it is ingested and destroyed by macrophages. Heparin is not detectable in plasma except in pathologic circumstances (e.g., mastocytosis). Commercially available unfractionated heparin (UFH), or simply *heparin*, is indicated for prevention and treatment of VTE, prevention and treatment of pulmonary embolism (PE), treatment of atrial fibrillation with embolization, diagnosis and treatment of disseminated intravascular coagulation, and prophylaxis and treatment of peripheral arterial embolism.

Heparin is extracted from porcine intestinal mucosa or bovine lungs; however, because of the high propensity of thrombocytopenia



• **Fig. 22.3** Triggers affecting platelet aggregation and their antagonists. Numerous agonists can mitigate platelet activation, which can be inhibited by drugs with corresponding mechanisms of action. Expression of the platelet receptor glycoprotein (GP) IIb/IIIa on the platelet surface causes fibrinogen to bind to the platelet and subsequent linking of the two platelets (aggregation). This is the final common pathway to platelet aggregation. ASA, Aspirin; DTIs, direct thrombin inhibitors; LMWH, low-molecular-weight heparin; SSRIs, selective serotonin reuptake inhibitors.



• **Fig. 22.4** Extrinsic and intrinsic pathways of the coagulation system. The coagulation system is divided into the intrinsic pathway and extrinsic pathway. The intrinsic or contact activation pathway is activated by trauma or infection, which causes inflammatory proteins to be released in the circulation. The main role of the extrinsic pathway is to initiate coagulation during hemostasis. In the presence of calcium, the activated forms of factors X and V catalyze the conversion of prothrombin to thrombin.

with the bovine lung derivative, only the porcine derivative is routinely employed in practice. Heparin serves as a catalyst that accelerates the rate of the thrombin-to-antithrombin III reaction by at least 1000-fold by serving as a catalytic template to which both bind, resulting in a ternary complex (heparin, thrombin, and antithrombin). Antithrombin III is a large protein (58,000 Da) that is synthesized in the liver and is known as a *suicide substrate*. Heparin is a high-molecular-weight complex mucopolysaccharide containing specific pentasaccharide units and approximately 45 monosaccharide side chains with a mean molecular mass of 12,000 Da (range 5,000 to 30,000 Da).^{28–30}

Most of the monosaccharide side chains of UFH are more than 18 monosaccharides long and are necessary to form the ternary complex. Heparin molecules that possess less than 18 monosaccharide units (less than 5400 Da) do not catalyze the thrombin-to-antithrombin III reaction. However, the heparin molecules that include less than 18 monosaccharides catalyze a conformational change on antithrombin III that inhibits the effects of factor Xa (Stuart factor) and does not require a ternary complex. LMWHs are generally about 4500 Da (range 1000 to 10,000 Da) and contain 15 monosaccharide units and do not form a ternary complex. Their anticoagulant activity is exhibited via factor Xa inhibition. Because factor Xa occurs earlier in the coagulation cascade, the inhibition of a single molecule of factor Xa prevents thousands of thrombin molecules from forming. The antifactor Xa/antifactor IIa ratio of UFH is 1:1; the anti-factor Xa/anti-factor IIa ratio of LMWH ranges from 2:1 (dalteparin) to 3.8:1 (enoxaparin). Heparin also inhibits the conversion of fibrinogen to fibrin and inhibits the activation of factor XIII, preventing the formation of a stable fibrin clot. LMWH is postulated to suppress von Willebrand factor, which increases platelet aggregation, and to stimulate the release of tissue factor pathway inhibitor, which inhibits factor Xa.

LMWHs include dalteparin (Fragmin) and enoxaparin (Lovenox). In contrast to LMWHs, UFH binds extensively to plasma proteins such as GPs, vitronectin, lipoproteins, fibrinogen, platelet proteins, acute-phase reactant proteins, and endothelial cells, yielding poor UFH bioavailability and an unpredictable effect. The predictable bioavailability of LMWHs allows for subcutaneous administration for all indications. UFH is administered subcutaneously for VTE prophylaxis but must be administered as a continuous infusion for serious indications such as MI and to minimize the risk of hemorrhage.

Heparin (UFH) is cleared faster and requires more frequent dosing or an intravenous continuous infusion. The half-life of UFH is approximately 30 to 60 minutes, whereas the half-life of LMWH is 4 to 5 hours, allowing for once-daily or twice-daily LMWH administration. The onset of action of heparin is within 6 hours of initiation of a continuous infusion. LMWH time to peak antifactor Xa activity is 2 to 5 hours. Each commercially available LMWH is synthesized by different mechanisms, possesses moderately different pharmacokinetic and pharmacodynamic characteristics, and has different FDA-approved indications and dose regimens; these agents are not interchangeable. [Table 22.15](#) presents the pharmacokinetic properties and dose parameters for all heparins.

Activated partial thromboplastin time (aPTT) is used to monitor the effects of heparin because it is sensitive to the inhibitory effects of thrombin, factor Xa, and factor IXa and correlates with heparin levels. When the concentration of plasma heparin is 0.1 to 1 U/mL, aPTT and thrombin time are prolonged. The goal of heparin therapy is to prevent unwanted clotting without an

increased risk of hemorrhage. This goal may be accomplished by maintaining aPTT between 1.5 and 2 times the upper limit of the control value. aPTT should not be used to monitor LMWHs. The effect of LMWHs may be monitored on the basis of antifactor Xa levels; however, because the relationship between antifactor Xa levels and clinical outcomes is tenuous, routine measurement is not indicated and should be reserved for special populations, such as patients with renal disease, obese patients, and underweight patients.²⁹

More recently, there has been a major change in the *United States Pharmacopeia* (USP) monograph of UFH. As a result of the heparin contamination problem encountered from 2007 to 2009, a new reference standard for heparin and a new test to determine potency were established by the FDA. These changes have resulted in an estimated 10% reduction in anticoagulant activity of UFH, which was validated. Because of this decrease in potency, the intravenous dose of UFH may need to be increased to achieve target aPTT, and more frequent or intensive aPTT monitoring may be required. No dose adjustment is needed for subcutaneous administration of UFH.³⁰

Adverse effects induced by UFH and LMWHs include bleeding, hematoma, early thrombocytopenia, delayed thrombocytopenia with or without white clot syndrome, hyperkalemia, osteoporosis (with prolonged use), and increase in liver enzyme tests (LETs). An increase in LETs may occur in 10% to 30% of patients receiving LMWHs or high-molecular-weight heparins. However, the increase in LETs seems benign and has not been associated with any cases of hepatic sequelae. Early-onset heparin-induced thrombocytopenia type 1 (HIT-1) manifests with a decrease in platelets of approximately 50,000/mm³. The decrease in platelets is transient and inconsequential. Delayed-onset heparin-induced thrombocytopenia type 2 (HIT-2) is due to the formation of anti-platelet antibodies between days 6 and 12.

If a patient has heparin-dependent antibodies present in plasma from previous heparin exposure, HIT-2 may occur at any time. HIT-2 is dependent on platelet factor-4 binding. These platelet antibodies aggregate and form the basis for the paradoxical heparin-induced white clot syndrome. The white clot syndrome is a medical emergency that may manifest as PE, MI, stroke, renal or hepatic thrombosis, or skin necrosis and gangrene. The diagnosis of HIT-2 is clinical and may be confirmed by several laboratory tests. Clinical diagnosis of HIT-2 includes a significant reduction in the platelet count of greater than 50%, a decrease in the platelet count to less than 100,000/mm³, or both. Ostensibly the risk of thrombocytopenia is greatest with UFH and lowest with LMWHs; however, LMWHs cannot be administered as an alternative to heparin because of greater than 95% cross-reactivity.³¹

Current treatment options for HIT-2 include the direct thrombin inhibitors (DTIs) argatroban, and bivalirudin, the anticoagulant danaparoid that is not currently available in the United States, selective factor Xa inhibitor fondaparinux, or a direct oral anticoagulant (DOAC) such as rivaroxaban, apixaban, dabigatran, or edoxaban.³¹

The antidote for heparin is protamine sulfate. Protamine sulfate is derived from the sperm of mature testes of salmon and related species. Protamine is electropositive and rapidly binds to the electronegative heparin to form salts that have no anticoagulant effect. Protamine also causes a dissociation of heparin-antithrombin III complexes in favor of a heparin-protamine complex. The recommended neutralizing dose of protamine is 1 mg for every 100 U of heparin, up to a total of protamine 50 mg per dose. Protamine should be administered by slow intravenous infusion over at least

TABLE 22.15 Pharmacokinetic Properties and Dosage Guidelines of Heparins

Heparin Formulation	Molecular Weight (Da)	Anti-Xa/ Anti-IIa Ratio	Half-Life (min)	DOSAGE	
				Prophylaxis	Treatment
Dalteparin (Fragmin)	4000–6000	2:1	119–139	General surgery: 5000 U every 24 hr Hip/knee orthopedic surgery: 5000 units once daily with initial dose administered ≥ 12 hours preoperatively or postoperatively once hemostasis is achieved or 2500 units pre- or postoperatively with a maintenance dose of 5000 units once daily Acute medical illness: 5000 U every 24 hr	200 U/kg every 24 hr or 100 U/kg every 12 hr Kidney impairment: No specific dosage adjustment recommended Extended VTE treatment in patients with cancer: Days 1–30: 200 U/kg every 24 hr Months 2–6: 150 U/kg every 24 hr Unstable angina or non-Q wave MI: 120 U/kg (maximum of 10,000 U) every 12 hr with concurrent aspirin therapy until clinically stable
Enoxaparin (Lovenox)	3500–5500	3.8:1	129–180	General surgery: 40 mg every 24 hr; for CrCl <30 mL/min use 30 mg every 24 hr Orthopedic surgery: 30 mg every 12 hr (TKR/THR); 40 mg every 24 hr (THR only); if CrCl <30 mL/min, use 30 mg every 24 hr Acute medical illness: 40 mg every 24 hr; if CrCl <30 mL/min use 30 mg every 24 hr	Acute DVT: 1 mg/kg every 12 hr or 1.5 mg/kg every 24 hr Kidney impairment: CrCl <30 mL/min use 1 mg/kg every 24 hr STEMI: Age <75 years: 30 mg IV bolus plus 1 mg/kg SQ every 12 hr Age ≥ 75 years: 0.75 mg/kg SQ every 12 hr NSTEMI: 1 mg/kg SQ every 12 hr in conjunction with oral aspirin
Fondaparinux (Arixtra)	1728	NA		General surgery (adults ≥ 50 kg): 2.5 mg daily beginning 6–8 hr after surgery Hip or knee orthopedic operations: 2.5 mg every 24 hr beginning 6–8 hr after surgery Acute medical illness: 2.5 mg every 24 hr	Weight ≤ 50 kg: 5 mg every 24 hr Weight 50–100 kg: 7.5 mg every 24 hr Weight >100 kg: 10 mg every 24 hr Kidney impairment: CrCl <30 mL/min: contraindicated
Unfractionated Heparin (UFH)	10,000–15,000	1:1	30–150*	5000 U every 8–12 hr	DVT/PE: IV: 80 units/kg (or 5000 units) IV push followed by continuous infusion of 18 units/kg/hr (or 1300 units/hr) SQ (Outpatient Treatment): Initial: 333 units/kg then 250 units/kg every 12 hr STEMI: Bolus of 60 units/kg (maximum: 5000 units), then 12 units/kg/hr (maximum: 1000 units/hr) as continuous infusion, with target aPTT of 1.5–2 times upper limit of control (50–70 sec) NSTEMI: Initial bolus of 60 units/kg (maximum of 5000 units) followed by 12 units/kg/hr (maximum of 1000 units/hr). Dosage adjustment to correspond to therapeutic range equivalent with target aPTT of 1.5–2 times upper limit of control (50–70 sec)

*Half-life of UFH has saturable binding, and half-life increases with doses more than 400 U/kg.

aPTT, Activated partial thromboplastin time; CrCl, creatinine clearance; DVT, deep vein thrombosis; IV, intravenous administration; MI, myocardial infarction; NA, not available; NSTEMI, non-ST segment elevation myocardial infarction; PE, pulmonary embolism; SQ, subcutaneous administration; STEMI, ST segment elevation myocardial infarction; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

1 to 3 minutes to prevent hypotension, bradycardia, or dyspnea. Patients who have previously received protamine-containing insulin, have undergone a vasectomy, or have a known sensitivity to fish or medications derived from fish (calcitonin-salmon, cold water fish oils containing omega-3 fatty acids, and oyster shell-derived calcium supplements) are at an increased risk for experiencing allergic reactions such as anaphylaxis and developing antiprotamine antibodies.²⁶ Excessive protamine may act as an anticoagulant, resulting in bleeding complications; a careful underdose strategy is suggested. There is no proven method for neutralizing LMWHs. Protamine seems to neutralize approximately 60% of the antifactor Xa activity of LMWHs. UFH may be the preferred parenteral anticoagulant in patients who are at risk for clinically significant bleeding, such as patients with end-stage renal disease receiving hemodialysis treatments.

Direct Thrombin Inhibitors

There are four highly specific parenteral DTIs and one orally available DTI. Dabigatran (Pradaxa), the only orally available DTI, is used for deep vein thrombosis (DVT) postoperative prophylaxis in knee and hip surgery patients, treatment of DVT and PE, and prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Parenteral DTIs include bivalirudin (Angiomax), which is indicated for unstable angina, and argatroban (Argatra), which is indicated for prophylaxis or treatment of thrombosis in patients with HIT-2. Desirudin (Iprivasc) and lepirudin (Refludan) are two additional parenteral DTIs that are no longer available on the US market. DTIs exert their anticoagulant effects by directly inhibiting the effects of thrombin on a sustained fibrin clot. One molecule of a DTI binds to one molecule of thrombin. DTIs are independent of antithrombin III reactions and are not inhibited by platelet factor IV. aPTT is used to monitor the effects of DTIs and is generally maintained at about 1.5 to 2.5 times the upper limit of the control.

The most common adverse effects of DTIs are minor and major hemorrhage. DTIs may cause allergic skin reactions and anaphylactic reactions manifesting with bronchospasm, stridor, and dyspnea. There are no proven antidotes for the parenteral DTIs. However, there may be a role for recombinant human factor VIIa (rFVIIa; NovoSeven) in DTI bleeding toxicities. rFVIIa is cloned from hamster kidney cells; it is a vitamin K-dependent GP (molecular mass 50 Da) structurally similar to human plasma-derived factor VIIa. rFVIIa can activate factor IX to IXa and factor X to Xa, converting prothrombin to thrombin and fibrinogen to fibrin and forming a hemostatic plug.

Argatroban is a synthetic agent derived from L-arginine that reversibly binds to the thrombin active site. It is administered through continuous intravenous infusion. The half-life of argatroban is 30 to 50 minutes. The route of elimination is primarily via the hepatic CYP3A4/5 isoenzyme system, and the potential for drug interactions exists with CYP3A4/5 inhibitors and inducers. There are four argatroban hepatic metabolites; only M1 is active. It is about threefold to fivefold weaker than the parent drug and is present at 0% to 20% relative to the parent. The recommended initial dose of argatroban is 2 mcg/kg/min of body weight up to 130 kg. aPTT should be attained 1 to 3 hours after initiation. The dose should be adjusted until steady-state aPTT is 1.5 to 3 times the initial baseline value but does not exceed 100 seconds at a maximum of 10 mcg/kg/min. In critically ill patients or patients with hepatic dysfunction, the initial dose of argatroban should be reduced to 0.2 mcg/kg/min or 0.5 mcg/kg/min. The effects of argatroban are not significantly influenced

by renal impairment, and dosage adjustments are unnecessary in this setting.

When used in combination with warfarin, especially at doses exceeding 2 mcg/kg/min, argatroban has the potential to prolong the INR beyond that of warfarin alone. However, argatroban exerts no additional effects on vitamin K-dependent factor Xa activity. Special warfarin dosing considerations are required when concomitantly using argatroban and warfarin.

Direct Oral Anticoagulant Agents

Although warfarin is very effective in preventing thromboembolic events, its narrow therapeutic index and pharmacogenomic variability impose the need for routine monitoring and dietary restrictions. Therefore, the quest continues for the development of an ideal anticoagulant of similar promising attributes of warfarin, but without the undesirable aspects, such as the risk of bleeding. Within a decade, four oral anticoagulants (OACs) have been made available on the American market: a DTI, dabigatran (Pradaxa), and three direct Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). A fourth direct Xa inhibitor, betrixaban (Bevyxxa), was approved in 2017 but remained on the market for just under 3 years before its production was discontinued. An overview of the pharmacology of the direct oral anticoagulants (DOACs)^{32–36} is provided in Table 22.16.

Dabigatran etexilate is a DTI. As a prodrug, dabigatran etexilate is rapidly converted to dabigatran upon oral administration and achieves a maximum plasma concentration (T_{max}) within 2 to 3 hours. When administered orally dabigatran etexilate has relatively low bioavailability of 7.2%, accounting for the high doses that are needed to maintain therapeutic plasma concentrations. The half-life of dabigatran is 14 to 17 hours. Dabigatran is predominantly excreted in the kidneys (up to 80%) and in the feces.³² Although its metabolism is independent of CYP, potential drug interactions with quinine, quinidine, verapamil, and with P-gp inhibitors and/or inducers have been reported. When dabigatran is used for stroke prevention in nonvalvular atrial fibrillation patients, the recommended dose is 150 mg twice daily. However, patients should receive 50% of the recommended dose (75 mg twice daily) for stroke prevention if CrCl falls between 15 to 30 mL/min to avoid dabigatran accumulation and potential risk of bleeding.³² The dose should be also reduced to 75 mg twice daily if the CrCl is 30 to 50 mL/min and the patient is on concomitant dronedarone or ketoconazole, and it should be avoided in patients who are taking any P-gp inhibitors with CrCl <30 mL/min or any patients who are taking any P-gp inducers such as rifampin. In patients who are diagnosed with acute DVT or PE and have received 5 to 10 days of appropriate parenteral anticoagulant, the dabigatran dose in patients with CrCl >30 mL/min is 150 mg twice daily and is not recommended for patients with CrCl <30 mL/min or patients with CrCl <50 mL/min who are taking concomitant P-gp inhibitor, or any patients that are taking P-gp inducers. For the prevention of DVT or PE after hip replacement surgery, patients should receive a one-time dose of 110 mg for the first day, followed by 220 mg daily, if CrCl > 30 mL/min. No dosing recommendation is available for patients with CrCl ≤ 30 mL/min. It should be avoided in patients on hemodialysis in all indications. Unlike warfarin, dabigatran does not require routine blood test monitoring and dietary restrictions. In the RE-LY trial comparing the efficacy and safety of dabigatran and warfarin, both drugs demonstrated a similar efficacy and safety profile. The rate of serious bleeding was similar between the two drugs and

dabigatran was associated with fewer strokes than warfarin.³⁷ After dabigatran's approval, a large number of reports of bleeding were submitted to the FDA's Adverse Events Reporting System (AERS) database, a postmarketing surveillance program. In the data assessment, dabigatran was associated with a lower risk of clot-related strokes, bleeding in the brain, and death than warfarin. However,

the study found an increased risk of major gastrointestinal bleeding with use of dabigatran compared with warfarin. The MI risk was similar for warfarin and dabigatran. This latest finding indicated that the observed bleeding rates associated with new use of dabigatran did not appear to be higher than the bleeding rates associated with the use of warfarin, which resonated with the

TABLE 22.16 Direct Oral Anticoagulants Indications, Dosage Guidelines, Pharmacokinetics, Cautions, and Reversal for Elective Surgery

	Apixaban	Rivaroxaban	Dabigatran
Brand name	Eliquis	Xarelto	Pradaxa
FDA indication(s)	Thromboembolism treatment and prophylaxis, stroke prevention in nonvalvular atrial fibrillation	Thromboembolism treatment and prophylaxis, stroke prevention in nonvalvular atrial fibrillation, reduction of risk of major cardiovascular and thrombotic vascular events	Thromboembolism treatment and prophylaxis, stroke prevention in nonvalvular atrial fibrillation
Dosage			
Stroke prevention in nonvalvular atrial fibrillation	5 mg twice daily (2.5 mg twice daily if two of the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL)	20 mg daily with evening meal (15 mg daily with evening meal if CrCl 15–50 mL/min)	150 mg twice daily (75 mg twice daily if CrCl 15–30 mL/min)
DVT/PE treatment	10 mg twice daily for 7 days then 5 mg twice daily	15 mg twice daily for 3 wk then 20 mg daily with food	150 mg twice daily (after 5–10 days parenteral anticoagulation)
DVT/PE prophylaxis	2.5 mg twice daily (If used for prevention of recurrent DVT or PE, start 6 months after previous treatment for DVT or PE)	10 mg daily	110 mg x 1 dose, 220 mg daily starting on the following day (after total hip replacement surgery)
Pharmacokinetics/Pharmacodynamics			
C _{max} (hr)	3–4	2–4	1–2
Bioavailability	50%	80%–100%	3%–7%
Volume of distribution (L)	21	50	50–70
Protein binding	87%	92%–95%	35%
Half-life (hr)	12	5–9; 11–13 elderly	12–17; 14–17 elderly
Clearance	25% renal, 75 % biliary	60% renal, 33% biliary	80% renal
Metabolism	CYP3A4	CYP3A4, CYP2J2	Hepatic glucuronidation
P-glycoprotein substrate	Yes	Yes	Yes
Drug interactions	Avoid with strong dual inhibitors of P-gp and CYP3A4 if already taking 2.5 mg twice daily	Avoid with strong CYP3A4 inhibitors or inducers; avoid with strong dual inducers of P-gp and CYP3A4; avoid with dual strong inhibitors of P-gp and CYP3A4	Avoid with P-gp inducers; avoid with P-gp inhibitors
Cautions			
Boxed warning	D/c therapy increases risk of thrombotic events; epidural or spinal hematomas may occur if used while receiving neuraxial anesthesia or spinal puncture	D/c therapy increases risk of thrombotic events; epidural or spinal hematomas may occur if used while receiving neuraxial anesthesia or spinal puncture	D/c therapy increases risk of thrombotic events Insert or remove a spinal epidural or lumbar puncture when anticoagulant effect is low
Contraindications	Active bleed, hypersensitivity, prosthetic heart valve	Active bleed, hypersensitivity	Active bleed, hypersensitivity, mechanical prosthetic heart valve
Reversal for elective surgery	High bleeding risk procedure: d/c at least 48 hr prior Low bleeding risk procedure: d/c at least 24 hr prior	D/c at least 24 hr prior	CrCl ≥ 50 mL/min, d/c 1–2 days prior CrCl < 50 mL/min, d/c 3–5 days prior

TABLE 22.16 Direct Oral Anticoagulants Indications, Dosage Guidelines, Pharmacokinetics, Cautions, and Reversal for Elective Surgery—cont'd

Edoxaban	
Brand name	Savaysa
FDA indication(s)	Stroke prevention in nonvalvular atrial fibrillation, treatment of DVT or PE
Dosage	
Stroke prevention in nonvalvular atrial fibrillation	60 mg daily for CrCl 51–95 mL/min 30 mg daily for CrCl 15–50 mL/min
DVT/PE treatment	After at least 5 days of initial therapy with a parenteral anticoagulant then 60 mg once daily or 30 mg once daily for CrCl 15–50 mL/min, weigh ≤60 kg, or on certain P-glycoprotein inhibitors
DVT/PE prophylaxis	N/A
Pharmacokinetics/Pharmacodynamics	
C _{max} (hr)	1–2
Bioavailability	62%
Volume of distribution (L)	107
Protein binding	55%
Half-life (hr)	10–14
Clearance	50% renal, 50% biliary/intestine/metabolism
Metabolism	Minimal through CYP enzymes
P-glycoprotein substrate	Yes
Drug interactions	When used for DVT or PE, maximal daily dose is 30 mg when used with certain P-gp inhibitors (verapamil, quinidine, or short term azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole)
Cautions	
Boxed warning	D/c therapy increases risk of thrombotic events; epidural or spinal hematomas may occur if used while receiving neuraxial anesthesia or spinal puncture; DO not give for nonvalvular atrial fibrillation with CrCl > 95 mL/min
Contraindications	Active bleed
Reversal for elective surgery	D/c at least 24 hr prior

CrCl, Creatinine clearance; CYP, cytochrome P450; d/c, discontinue; DVT, deep vein thrombosis; FDA, US Food and Drug Administration; IV, intravenous administration; N/A, not available; P-gp, p-glycoprotein; PE, pulmonary embolism.

RE-LY study.³⁸ Dabigatran is contraindicated in patients with active bleeding, patients with mechanical prosthetic heart valves, and patients with serious hypersensitivity to any components of its formulation.³² An overview of dabigatran pharmacology is provided in Table 22.16.

Rivaroxaban is a direct factor Xa inhibitor with a competitive and reversible binding to factor Xa. Unlike dabigatran, rivaroxaban has a high oral bioavailability of 60% to 80% and a T_{max} of 3 hours upon oral ingestion. Interestingly, studies had shown that rivaroxaban exhibited a slightly lower anti-Xa activity in fasting patients compared with patients who were fed; therefore, it is recommended to administer with food for a rivaroxaban dose equal or greater than 15 mg. For patients who cannot swallow whole tablets, the manufacturer's labeling states the 10 mg, 15 mg, and 20 mg tablets may be crushed and mixed with water or applesauce. The mixture is stable for up to 4 hours. The half-life of rivaroxaban is between 5 to 9 hours, with approximately 33% of the drug excreted unchanged renally and 66% metabolized in the

liver primarily via CYP. Because of its association with the CYP system, it is subjected to drug interactions of CYP3A4 enzymes, and it is also affected by P-gp inhibitors and/or inducers. For treatment of VTEs, the recommended dosage is 15 mg twice daily with food for 3 weeks followed by 20 mg once daily with food for a total duration of 3 months in patients with provoked DVT or ≥3 months with unprovoked DVT depending on the patient's risk for bleeding and recurrent thromboembolism. In selected patients, rivaroxaban can be used for up to 6 to 12 months after the initial treatment for further reduction of recurrent DVT or PE. Initiation of rivaroxaban for postoperative DVT prophylaxis should start within 6 to 10 hours postoperatively with 10 mg daily for 12 to 14 days in knee replacement and 35 days in hip replacement. Lastly, for patients with nonvalvular atrial fibrillation requiring anticoagulation for stroke prevention, the manufacturer recommends taking 20 mg daily of rivaroxaban with the evening meal. Similar to dabigatran, rivaroxaban requires dosage adjustment in patients with renal impairment. In patients who are treated for

DVT or PE or in patients with postoperative prophylaxis, the use of rivaroxaban should be avoided if CrCl is less than 30 mL/min. In patients with nonvalvular atrial fibrillation, the dosage should be reduced to 15 mg once daily if CrCl is between 15 and 50 mL/min and avoided in patients with CrCl less than 15 mL/min. It should be avoided in patients on hemodialysis in all indications. Caution should be exhibited when rivaroxaban is administered with a strong CYP3A4 and P-gp inhibitor or inducer.³³ In the ROCKET-AF trial comparing the efficacy and safety profile of rivaroxaban and warfarin in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. In the study, both drugs demonstrated similar risk of major bleeding that required blood transfusion. However, rivaroxaban was associated with less frequent intracranial hemorrhage and fatal bleeding compared with warfarin.³⁹ Rivaroxaban is contraindicated in patients with active bleeding or patients with hypersensitivity to any components of its formulation.³³ The manufacturer's recommended dosages regarding different indications is outlined in Table 22.16.

Apixaban is an oral direct factor Xa inhibitor with a reversible binding. Upon oral administration, it achieves T_{max} approximately within 3 hours with an oral bioavailability of 50%. Apixaban has a half-life of 9 to 14 hours. Similar to rivaroxaban, the drug is metabolized in the liver via a CYP-dependent pathway, followed by elimination of 25% through the kidneys and the remainder into the feces. It is affected by CYP3A4 and P-gp inducers and/or inhibitors. For stroke prevention in patients with nonvalvular atrial fibrillation, the manufacturer recommends to administer apixaban 5 mg twice daily, unless the patient has any two of the following patient-specific characteristics, including age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL; then reduce dosage to 2.5 mg twice daily. For postoperative VTE prophylaxis, it is recommended to administer apixaban 2.5 mg twice daily beginning 12 to 24 hours postoperatively for 35 days in hip replacement and 12 days in knee replacement. For the treatment of DVT or PE, the recommended dose is 10 mg twice daily for 7 days, followed by 5 mg twice daily for ≥ 3 months. For patients who require extended therapy past the initial 3-month period, consider a reduced dose of 2.5 mg twice daily. If apixaban is administered concomitantly with a strong CYP3A4 and P-gp inhibitor such as clarithromycin, ketoconazole, itraconazole, or ritonavir, the dosage should be reduced to 2.5 mg twice daily, if the patient was previously indicated for 5 mg twice daily. Patients who are to be given apixaban 2.5 mg twice daily for prevention of recurrent DVT or PE or for meeting the previously mentioned dose reduction criteria should not be receive strong CYP3A4 and P-gp inducers concomitantly because of the risk of subtherapeutic concentrations.³⁴ Compared with warfarin in patients with nonvalvular atrial fibrillation and prior history of stroke in the ARISTOTLE trial, apixaban was shown to be superior to warfarin. As illustrated in the study, apixaban was associated with a significant reduction of stroke and systemic embolism compared with warfarin.⁴⁰ In addition to its efficacy, apixaban demonstrated a safety profile superior to that of warfarin, such that apixaban was associated with less frequent intracranial bleeding, major or nonmajor bleeding, and mortality of any cause. Similar to all anticoagulants, apixaban is contraindicated in patients with active bleeding and patients with hypersensitivity to any components of its formulation.

Edoxaban (Savaysa), approved in 2015 was the third selective factor Xa inhibitor to join the US market.^{35,36} Similar to rivaroxaban, it directly binds to factor Xa and prevents the formation of a

clot. Edoxaban has an oral bioavailability of 62%, and the maximal serum concentration is achieved within 1 to 2 hours following administration. Food does not affect its absorption. It is 55% protein bound and is minimally metabolized by CYP enzymes. It is a substrate for the P-gp transporter. Edoxaban's primary active metabolite (M4) comprises of less than 10% of the concentration of the parent drug. It is primarily eliminated as an unchanged drug in the kidneys ($\sim 50\%$) as well as the biliary and intestines. Half-life of edoxaban is around 10 to 14 hours. For stroke prevention in nonvalvular atrial fibrillation, the recommended dose is 60 mg once daily for patients with CrCl > 50 mL/min and 30 mg once daily for those with CrCl of 15 to 50 mL/min. However, edoxaban is contraindicated in patients with CrCl above 95 mL/min. For DVT or PE, after 5 to 10 days of parenteral anticoagulant treatment, patients should be started on 60 mg once daily if CrCl > 50 mL/min and 30 mg once daily for those with CrCl of 15 to 50 mL/min, body weight ≤ 60 kg, or concomitant use of P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole).³⁵ Edoxaban was compared to warfarin in the ENGAGE AF-TIMI 84 trial for the prevention of stroke in patients with nonvalvular atrial fibrillation. Patients enrolled in the study were randomized to receive warfarin, edoxaban 30 mg daily, or edoxaban 60 mg daily. Edoxaban 60 mg dose was proven to be superior to warfarin in reducing the risk of stroke or systemic embolism, while edoxaban 30 mg was found to be noninferior to warfarin in the aforementioned endpoints. Both doses of edoxaban was associated with lower risks of death due to cardiovascular causes and lower risks of major bleeding events.^{35,41}

As for betrixaban, it has a 34% bioavailability, and its absorption is significantly decreased by concomitant administration with food. Its maximal serum concentration is reduced by 70% if taken with a low-fat meal and by 50% if taken with a high fat meal. Maximal serum concentration is achieved within 3 to 4 hours after administration. Betrixaban is 60% protein bound, and a small percentage (15%, 18%) undergoes CYP-independent hydrolysis to become inactive metabolites. It has a half-life of 19 to 27 hours and is primarily excreted in the stool (85%) and urine (15%). It is also a substrate for the P-gp. Betrixaban is only approved for the prevention of venous thromboembolism, and the recommended dose is 160 mg, followed by 80 mg daily for 35 to 42 days. For patients with CrCl between 15 and 29 mL/min, the recommended dose is 80 mg, followed by 40 mg daily for 35 to 42 days.³⁶ Betrixaban was compared to enoxaparin for venous thromboembolism prophylaxis in the APEX trial. Patients admitted to the hospital for medical illness were randomized to receive enoxaparin 40 mg subcutaneously for 10 ± 4 days or betrixaban for 35 to 42 days. Betrixaban significantly reduced the risks of deep vein thrombosis, pulmonary embolism, or death due to venous thromboembolism. Rates of major bleeding events were similar between the two groups.⁴²

A list of the recommended dosages for different indications is provided in Table 22.16.

Warfarin (Coumadin)

Warfarin (Coumadin) is an OAC indicated for prophylaxis and treatment of venous thrombosis, PE, thromboembolic complications associated with atrial fibrillation and cardiac valve replacement, and as an adjunct in the treatment of coronary occlusion. Warfarin is also used to reduce the risk of death, reinfarction, and thromboembolic events such as stroke or systemic embolization after MI. Warfarin is a racemic mixture; the (S)-isomer has a

half-life of 2 days, and the less potent (R)-isomer has a half-life of 1.3 days; warfarin is administered once daily. The full anticoagulant effect of warfarin has a delayed onset of 5 days, necessitating overlap with a parenteral heparin agent when rapid anticoagulation is preferred for at least 5 days.

The initial dose of warfarin for a majority of patients should be the expected maintenance dose, which is usually 5 to 10 mg. Loading doses of 10 mg for 2 days are only recommended for sufficiently healthy patients who are treated as outpatients followed by dosage based on INR.²⁹ Warfarin starting doses of less than 5 mg may be most appropriate in elderly patients. Warfarin interferes with the hepatic synthesis of vitamin K–dependent clotting factors II, VII, IX, and X and endogenous anticoagulant proteins C and S. The time to complete anticoagulation with warfarin is not immediate. Inhibition of coagulation factors begins 12 to 24 hours after administration; however, the complete antithrombotic effects of warfarin may not occur until 5 to 7 days after initiation of therapy.

The INR is the standard for monitoring warfarin therapy. Prothrombin time (PT) as a tool for monitoring warfarin therapy is problematic because thromboplastin reagents vary in their responsiveness to warfarin-induced reduction in clotting factors, a variability that depends on their method of preparation. The INR is a *mathematical correction* of the results of the one-stage PT that standardizes the reporting of PT determinations worldwide. The INR takes into account the sensitivity of the thromboplastin used in each specific laboratory to determine the PT. The target INR range for warfarin in most clinical scenarios is 2 to 3. The INR should be used exclusively to indicate doses of warfarin clinically; however, the PT should be reviewed in conjunction with the INR to aid in detecting laboratory errors in calculation or assay methodology.

Hemorrhage is the most common adverse effect associated with warfarin and ranges from minor to life-threatening major bleeding. Bleeding manifestations may include ecchymoses, petechiae, purpura, melena, hematochezia, hematuria, hemoptysis, hematemesis, epistaxis, or gingival bleeding. Because warfarin inhibits protein C (half-life 8 hours) and protein S (half-life 30 hours), which have shorter half-lives than factors II (half-life 60 hours), IX (half-life 24 hours), and X (half-life 72 hours), there is a risk of a paradoxical hypercoagulability, thrombus formation, and skin necrosis with gangrene. The procoagulant effect of warfarin can be enhanced in patients who have protein C and protein S deficiency. To minimize the immediate procoagulant effect of warfarin, an overlap of 5 days with a parenteral anticoagulant is warranted. Purple toe syndrome, caused by the release of atheromatous plaque emboli and cholesterol-rich microembolization, occurs approximately 3 to 10 weeks after initiation of coumarin therapy. Purple toe syndrome is reversible and is typically characterized by a purplish or mottled discoloration of the plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs. Oral or parenteral vitamin K₁ (phytonadione) may be administered to reverse the anticoagulant effects of warfarin.

Many factors such as diet, disease states, and drugs can alter the pharmacologic characteristics and effects of warfarin.²⁹ Patients should be counseled to eat a healthy and consistent diet. An increased intake of vitamin K–containing supplements and foods, such as green leafy vegetables, may result in a reduced anticoagulant response, decreased INR, and subsequently treatment failure such as an embolism. Conversely, abrupt decreases in vitamin K dietary intake may result in an increased anticoagulant

response with an increased INR and subsequent risk of hemorrhage. Hepatic disease and, to a lesser extent, renal disease may decrease elimination of warfarin and increase the effects of warfarin. A plethora of drugs can increase or decrease the effects of warfarin. It is prudent to measure the INR frequently when factors that interact with warfarin are added to a patient's regimen. Table 22.17 lists selected significant warfarin drug interactions.

The role of genetic polymorphism in the management of warfarin has been the focus of interest in more recent studies. CYP2C9, which plays an integral role in the metabolism of the S-isomer of warfarin, and VKOR complex subunit 1 (VKORC1), the gene that determines the activity of vitamin K epoxide reductase, both undergo genetic polymorphism leading to variances in warfarin responses between patients. Studies have shown that testing for a patient's genetic type can lead to decreased major bleeding or thromboembolic events resulting in hospital admission; however, current guidelines recommend against the *routine use* of pharmacogenetic testing for guiding dose administration of vitamin K antagonists (VKAs).²⁹ Genetic test kits (e.g., GeneMedRx) are available for purchase, FDA approved, and covered by insurance plans; dosage guidelines are available in the product package insert.

Because warfarin is a high-risk medication that can significantly interact with many medications, requires frequent INR

TABLE 22.17 Selected Significant Drug Interactions With Warfarin

Precipitant Drug	Mechanism
Amiodarone Cimetidine Lovastatin Metronidazole Omeprazole Quinidine TMP-SMX	These agents may increase anticoagulant effect of warfarin by inhibiting hepatic cytochrome P450 isozymes (CYP2C9, CYP3A4, or CYP1A2) involved in its metabolism; risk of bleeding may be increased
Chloral hydrate Loop diuretics Nalidixic acid NSAIDs	These agents may increase anticoagulant effect of warfarin by displacement from protein-binding sites (albumin); risk of bleeding may be increased
Antimicrobials NSAIDs Salicylates	These agents may increase anticoagulant effect of warfarin by inhibiting gastrointestinal vitamin K or by inhibiting platelet aggregation; risk of bleeding may be increased
Barbiturates Carbamazepine Oxcarbazepine Etretinate Glutethimide Rifampin Rifabutin	These agents may decrease anticoagulant effect of warfarin by induction of hepatic cytochrome P450 isozymes (CYP2C9, CYP3A4, or CYP1A2) involved in its metabolism; lack of warfarin efficacy and thrombosis may occur
Cholestyramine Estrogens Oral contraceptives Spironolactone Sucralfate Thiazide diuretics Vitamin K	These agents may decrease anticoagulant effect of warfarin by various mechanisms; lack of warfarin efficacy and thrombosis may occur

NSAIDs, Nonsteroidal antiinflammatory drugs; TMP-SMX, trimethoprim-sulfamethoxazole.

monitoring, and is pharmacokinetically challenging to determine correct dose, pharmacist-based warfarin clinics with physician supervision and collaboration have become a standard of best practice. More than 1500 such clinics are active in the United States today.

Direct Oral Anticoagulants and Drug Interactions

Warfarin, as mentioned previously, presents the potential for several drug interactions because of its metabolism via CYP2C9, CYP1A2, CYP3A4, and CYP2C19. In addition to CYP metabolism involving rivaroxaban and apixaban, the DOACs (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) are P-gp substrates. P-gp is a drug transporter found in the gastrointestinal enterocytes and hepatocytes. P-gp works by pumping the drug back into the intestinal lumen, which consequently reduces the bioavailability and the plasma concentration of orally administered drugs. These drug transporters are also found in the kidneys and participate in drug elimination via this route. Therefore, P-gp inhibitors can significantly increase the bioavailability and plasma concentrations, and inducers can significantly decrease the bioavailability and plasma concentrations of drugs metabolized via this pathway. Other substrates of P-gp include colchicine, cyclosporine, digoxin, fexofenadine, indinavir, morphine, and sirolimus. Inhibitors of the P-gp include amiodarone, clarithromycin, erythromycin, ketoconazole, quinidine, saquinavir, verapamil, and grapefruit juice. P-gp inducers include carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John's wort, tipranavir, and trazodone. It is important for the clinician to be aware of any concomitant P-gp inhibitors or inducers when a patient is taking one of the DOACs because of the risk of toxicity or ineffectiveness, depending on inhibition or induction of this transporter system.^{43–46} Table 22.18 shows the most common P-gp substrates, inhibitors, and inducers.

Potential Reversal Agents for Direct Oral Anticoagulants

The advent of the DOACs heralds the discussion for potential reversal agents in the event of clinically severe bleeding. An important advantage of warfarin over the new OACs is the availability of an FDA-approved oral and parenteral vitamin K antidote with well-established dose guidelines and the FDA-approved four-factor PCC (Kcentra) for urgent reversal of warfarin-induced major bleeding. Since 2015, idarucizumab (Praxbind) was approved for the reversal of dabigatran when emergency surgical procedures are necessary or patients present with life-threatening bleeds. Idarucizumab is a humanized monoclonal antibody and works by binding to dabigatran and neutralizing it within minutes. It comes as

two vials (2.5g each) and can be given as intravenous continuous infusion or bolus. Aseptic technique must be practiced when handling idarucizumab, and a preexisting line must be flushed with normal saline prior to administration. In a prospective, cohort study, the majority (>90%) of the patients achieved reversal of the anticoagulation effect of dabigatran, and the average time to recovery of bleeding event was 11.4 hours. Dabigatran should be started 24 hours after the last dose of idarucizumab to minimize the risks of clotting. Patients need to be monitored for potential thromboembolic event and hypersensitivity reaction.^{47,48} Andexanet alfa (Andexxa), the newest of the reversal agents, received FDA approval in 2018 for reversal of rivaroxaban and apixaban in cases of life-threatening bleeding. While not approved for reversal of edoxaban, it is likely effective for edoxaban reversal as well. Andexanet alfa was studied in the ANNEXA trial. The study focused on efficacy of andexanet alfa in the reversal of rivaroxaban and apixaban and found that it reduces the levels of anti-Xa activity within 2 to 5 minutes after administration of the bolus dose. The effect of andexanet alfa continues for up to 2 hours after completion of therapy. It is started with a bolus dose of 400 to 800 mg at a target rate of 30 mg/min followed by an infusion of 4 to 8 mg/min for up to 120 minutes. Patients should be monitored for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce the risk of thromboembolism, anticoagulant therapy should be resumed as soon as medically appropriate after andexanet alfa use.⁴⁹

Recombinant factor VIIa (Novo Seven) initiates thrombin generation by activating factor X, thus promulgating the coagulation cascade. Prothrombin complex concentration (PCC) products are concentrated pooled plasma products that typically contain clotting factors. These factors are generally not activated and will require activation via the coagulation cascade. In addition, some PCC products also contain proteins C and S, and in some cases, a minimal amount of heparin and antithrombin to prevent thrombotic complications. Three-factor PCC (Bebulin and Profilnine) contains trace or subtherapeutic amounts of nonactive factor VII relative to factors II, IX, and X. Four-factor PCC (Kcentra) contains relatively large amounts of four nonactive vitamin K-dependent procoagulant factors II, VII, IX, and X. Unlike previously mentioned PCC products, activated PCC (FEIBA) contains activated factor VII and factors II, IX, X, albeit mainly in non-activated form. Therefore, activated PCC (FEIBA) combines the effect of both recombinant factor VIIa (Novo Seven) and four-factor PCC (Kcentra).^{50–55} These agents are not considered antidotes and not approved by the FDA for the reversal of the DOACs. An overview of different hemostatic agents for reversal of DOACs is summarized in Table 22.19.

If nonurgent reversal is required due to an elective surgery or invasive procedure, it is recommended to hold the DOACs for a certain period of time before the procedure depending on the patient's risk for bleeding and the patient's renal function. Dabigatran should be discontinued 1 to 2 days before elective surgery in patients with CrCl >50 mL/min and 3 to 5 days in patients with CrCl <50 mL/min. Longer times should be considered for patients undergoing major surgery, spinal surgery, or insertion of spinal or epidural catheter or port.³² The rivaroxaban package insert recommends holding rivaroxaban for 24 hours before a procedure; however, some have recommended holding rivaroxaban for minimum of 3 days before surgery in patients with CrCl >50 mL/hr and 5 days in patients with CrCl <50 mL/min. The risk of bleeding should be weighed against the urgency of the procedure.^{33,56} For patients who are taking apixaban and are scheduled for surgery

TABLE 22.18 P-Glycoprotein Substrates, Inhibitors, and Inducers

Substrates	Inhibitors	Inducers
Apixaban	Amiodarone	Carbamazepine
Colchicine	Clarithromycin	Rifampin
Cyclosporine	Erythromycin	St. John's wort
Dabigatran	Grapefruit juice	Tipranavir
Digoxin	Ketoconazole	
Fexofenadine	Quinidine	
Indinavir	Saquinavir	
Morphine	Verapamil	
Rivaroxaban		
Sirolimus		

TABLE 22.19 Potential Reversal Agents for Direct Oral Anticoagulants

	Idarucizumab	Andexanet Alfa	Recombinant Activated Factor VIIa	Three-Factor PCC	Four-Factor PCC	Activated PCC
Brand name	Praxbind	Andexxa	Novo Seven	Bebulin or Profilnine	Kcentra	FEIBA
Onset	Minutes	2 minutes	10 min	10 min	10 min	10 min
Duration of action	At least 24 hours	At least 22 hours	2–6 hr	12–24 hr	6–8 hr	12–24 hr
Dosage	5 g (given as two 2.5 g doses within 15 minutes)	400–800 mg IV, varies by dose and timing of factor Xa inhibitor given	Hemophilia with inhibitors: 90 mcg/kg/2 hr Factor VII deficiency: 15–30 mcg/kg/4–6 hr Acquired hemophilia: 70–90 mcg/kg/2–3 hr	Hemorrhage: Minor: 25–35 units/kg Moderate: 40–55 units/kg Major: 60–70 units/kg	INR 2 to <4: 25 units/kg INR 4–6: 35 units/kg INR >6: 50 units/kg	50–100 units/kg/6–12 hr
Monitoring	Control of bleeding	Control of bleeding; signs of clotting; anti-factor Xa activity	Control of bleeding	Factor IX level, PT, PTT, INR (in warfarin reversal)	INR	Control of bleeding
Cost in a 70-kg patient	\$5000	\$13,200–\$26,400, Varies by dose given	\$2,000–\$10,000, varies with indications	\$2000–\$5000, varies with severity of bleeding	\$2000–\$4000, varies with level of INR	\$6000–\$12,000

INR, International normalized ratio; PCC, prothrombin complex concentration.

or invasive procedure with moderate-to-high risk of bleeding, it is recommended for apixaban to be held for 48 hours before the procedure. If the procedure carries a low risk of bleeding, then apixaban can be held for 24 hours before the procedure.³⁴ As for edoxaban, the package insert recommends to withhold therapy for at least 24 hours prior to surgical procedures. If surgery needs to be performed right away, the benefits of the surgery need to be weighed against the risks of bleeding.³⁵

Four-Factor Prothrombin Complex Concentrate (Kcentra) for Warfarin Reversal

In 2013, the FDA approved the four-factor PCC (Kcentra) for the urgent reversal of warfarin anticoagulation in adults with acute major bleeding. Like plasma, Kcentra is used in conjunction with the administration of vitamin K to reverse the anticoagulation effect and stop the bleeding. Unlike the plasma counterpart, Kcentra does not require blood group typing or thawing, adding the additional advantage for dosage convenience and ease. Kcentra dosage is individualized based on the pretreatment INR. For pretreatment INR of 2 to <4, Kcentra is to be administered at 25 units/kg to a maximum dose of 2500 units. For pretreatment INR of 4 to 6, Kcentra is to be administered at 35 units/kg to a maximum dose of 3500 units. For pretreatment INR of >6, Kcentra is to be administered at 50 units/kg to a maximum dose of 5000 units. In addition to administration ease, Kcentra is given in a significantly lower volume than plasma, providing an alternative for those patients who may not tolerate the volume of plasma required for warfarin anticoagulation reversal. Similar to all procoagulants, Kcentra is associated

with the occurrence of blood clots; therefore, it carries a boxed warning regarding the risk of thromboembolic events, requiring close monitoring for signs and symptoms of blood clotting complications.^{57,58}

2021 CHEST Anticoagulation Guidelines Update

The CHEST Guideline is a publication compiled by the ACCP and provides evidence-based recommendations on various VTE states, including PE and DVT. The most recent edition of the guidelines was published in 2021.²⁹ For acute DVT in the leg or PE and no history of cancer, the guidelines recommend initial treatment with any of the DOACs, including dabigatran, apixaban, edoxaban, or rivaroxaban.²⁹ Oral Xa inhibitors apixaban, edoxaban, or rivaroxaban are recommended in patients with cancer who present with a DVT or PE, although LMWH or apixaban may be preferred in patients with luminal gastrointestinal malignancies due to a decreased risk for gastrointestinal bleeding. For a DVT or PE provoked by a major or minor transient risk factor, 3 months of treatment is recommended. For an unprovoked event or an event provoked by a persistent risk factor, extended treatment with no scheduled stop date is recommended. However, it is important that bleeding and thromboembolism risk are continually reassessed to identify the optimal duration of therapy when extended therapy is administered.⁵⁹

Benefits for the use of the DOACs include the fast onset of action, lack of need for continuous drug therapy monitoring, and the convenience of not requiring bridging with rivaroxaban and apixaban. Barriers to their use include the limited evidence

regarding their use in renally impaired patients, drug interactions, and cost. In patients with mechanical valves or valvular atrial fibrillation, liver dysfunction, or severe renal impairment, warfarin would generally be the drug of choice.⁴³

Antiplatelet Agents

Aspirin

In platelets, the prostaglandin derivative thromboxane A_2 is a major inducer of platelet aggregation and vasoconstriction. Aspirin is hydrolyzed to salicylic acid and inhibits prostaglandin production by acetylating cyclooxygenase, the initial enzyme in the prostaglandin biosynthesis pathway. This inhibition of platelet aggregation lasts for the life of the platelet, which is approximately 7 to 10 days. By inhibiting platelet aggregation, aspirin increases bleeding times. Low doses of aspirin inhibit platelet aggregation, whereas larger doses inhibit cyclooxygenase in arterial walls, which interferes with PGI_2 production. PGI_2 is a potent vasodilator and inhibitor of platelet aggregation. Lower doses are preferred over higher doses in preventing coronary heart disease.^{22,23}

Aspirin has many indications including fever and pain associated with headaches, neuralgias, myalgias, and arthralgias. Antithrombotic indications for aspirin include reducing the risk of thrombosis, such as in the primary and secondary prevention of nonfatal or fatal MI in patients with or without previous MI or unstable angina, and preventing recurrent transient ischemic attacks (TIAs) or stroke. The dose of aspirin for its analgesic, anti-inflammatory, and antipyretic effects is considered high dose and may be 325 to 650 mg up to every 4 hours daily as needed. The dose of aspirin for its antithrombotic indications is considered low dose; the range for prevention of MI is 81 to 325 mg daily and for TIA or stroke is 75 to 100 mg daily. Of patients taking aspirin as an antithrombotic, 25% may be genetically prone to aspirin resistance, and higher doses may be necessary to overcome resistance (e.g., 500 mg to 1.5 g daily). Since 2016, a 24-hour extended release (ER) formulation of aspirin (Durlaza) became available on the market. ER aspirin is only indicated for chronic CAD and history of ischemic stroke or TIA. The recommended dose for both indications is 162.5 mg daily.⁶⁰ Aspirin resistance is best detected via bleeding time tests; however, these tests are not yet validated or standardized, and they are not routinely employed in clinical practice.

Aspirin-induced adverse effects are dose dependent and include peptic ulcer disease, renal dysfunction, increased blood pressure, tinnitus, pulmonary dysfunction, and bleeding. The risk of clinically significant hemorrhage with aspirin (e.g., gastrointestinal bleeds) is dose dependent. However, any dose of aspirin carries a risk of major bleeding compared with placebo controls. Patients should be counseled on the signs and symptoms of bleeding, which may include anemia, abnormal bruising, epistaxis, bleeding of the gums, dizziness and lightheadedness associated with low blood pressure, and rapid heart rate. Aspirin, especially at high doses, can induce or exacerbate asthma by inhibiting bronchodilatory prostaglandins (PGE_2 and PGI_2) and can exacerbate dyspnea in patients with chronic obstructive pulmonary disease. Aspirin is contraindicated in patients who have a history of allergy, especially anaphylaxis to NSAIDs. Patients with rhinorrhea, nasal polyps, and aspirin-induced or NSAID-induced dyspnea are at greatest risk of aspirin-induced or NSAID-induced anaphylaxis. Aspirin should not be administered to children or teenagers with viral infections because of the risk of Reye syndrome.

An important drug–drug interaction between ibuprofen and aspirin has been identified. Ibuprofen interferes with aspirin access to the platelet serine-binding site and inhibits the pharmacologic effect of aspirin. This drug interaction occurs during single ingestion when ibuprofen is administered before aspirin or with long-term use of ibuprofen and aspirin regardless of whether ibuprofen is administered before or after aspirin. When aspirin is ingested 30 minutes after naproxen, naproxen can significantly interfere with aspirin's ability to inhibit thromboxane A_2 . Diclofenac (Voltaren) and celecoxib (Celebrex) do not seem to interact with aspirin; other NSAIDs have not been studied.^{61,62} The combination of aspirin and NSAIDs may lead to a high risk of life-threatening gastropathy, especially in elderly patients or patients using concomitant antithrombotic agents. Aspirin and NSAIDs inhibit gastrointestinal vasodilatory prostaglandins (PGE_2 and PGI_2), increasing the accumulation of aggressive factors (acid) and decreasing the supply of defensive factors (sodium bicarbonate). Patients should be immediately placed on gastropathy prophylaxis with proton pump inhibitors (PPIs) (e.g., omeprazole, pantoprazole, esomeprazole, or lansoprazole) or misoprostol (Cytotec).

Dipyridamole

Dipyridamole is a vasodilator and platelet adhesion inhibitor. It has been postulated that patients with prosthetic heart valves have abnormally shortened platelet survival time. Dipyridamole lengthens the abnormally shortened platelet survival time in a dose-dependent manner. The primary effect of dipyridamole is to inhibit cGMP-specific phosphodiesterase, increasing cGMP levels and augmenting the effects of nitric oxide. Dipyridamole weakly inhibits red blood cell, endothelial cell, and platelet uptake of the platelet activity inhibitor adenosine and inhibits the formation of thromboxane A_2 ; this effect occurs in a dose-dependent manner (0.5 to 1.9 mcg/mL). This uptake inhibition results in dipyridamole inhibiting platelet function by inhibiting cyclic adenosine 3',5'-monophosphate (cAMP)-specific phosphodiesterase, which leads to increased cellular concentrations of cAMP within platelets, preventing platelet aggregation by stimuli such as collagen and ADP. Dipyridamole does not alter PT levels but can increase the platelet bleeding time.

Dipyridamole (Persantine) is indicated only as an adjunct to warfarin in the prevention of postoperative thromboembolic complications of cardiac valve replacement. Intravenous dipyridamole, occasionally used for cardiac exercise stress testing, may decrease blood pressure and increase heart rate and cardiac output; this effect is generally not seen with the oral dosage form. Dipyridamole is eliminated via hepatic conjugation and glucuronidation; it does not undergo hepatic CYP elimination. Dipyridamole has a weak metabolite and undergoes negligible renal elimination. The half-life of dipyridamole is 13 hours. Adverse reactions are transient and include headache, dizziness, hypotension, and abdominal distress. Rarely, dipyridamole has aggravated angina symptoms; the intravenous form has precipitated acute myocardial ischemia. Dipyridamole can potentiate the effects of intravenous adenosine, causing fatal asystole or sustained ventricular tachycardia; a decreased dose of adenosine should be used when treating paroxysmal supraventricular tachycardia.

Aggrenox is a combination gelatin capsule containing 200 mg of extended-release dipyridamole with 25 mg of aspirin and is indicated to reduce the risk of stroke for patients who have had TIAs or complete ischemic strokes. Steady-state dipyridamole peak and trough plasma levels are 2 and 0.5 mcg/mL, allowing for dipyridamole to achieve its effects on cAMP and cGMP throughout

the dosing interval; this is not likely to occur with prompt-release dipyridamole. Dipyridamole requires an acidic environment for gut absorption; Aggrenox contains tartaric acid, allowing for maximal bioavailability in patients who have gut hypochlorhydria or achlorhydria (e.g., elderly patients).

The second European Stroke Prevention Study (ESPS-2) showed that dipyridamole modified-release formulation, 200 mg given twice daily, is effective in the secondary prevention of stroke and TIA compared with a placebo and that coadministration with aspirin, 25 mg twice daily, provides an additional benefit.⁶² ESPS-2 showed that the relative risk reduction for stroke with aspirin administration compared with a placebo was 18.1% ($P = .013$); for modified-release dipyridamole, the relative risk reduction was 16.3% ($P = .039$); and with the combination, it was 37% ($P < .001$). Aggrenox must not be substituted with prompt-release dipyridamole and aspirin. The recommended dosage of Aggrenox is one capsule twice daily, swallowed whole. Because of increased risk of headache, it may be advisable to start with one capsule daily at bedtime and low-dose aspirin in the morning for up to 1 week until tolerated before increasing the Aggrenox dose to twice daily.⁶³ The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial compared the efficacy of triple antiplatelet therapy (aspirin, clopidogrel, and dipyridamole) with that of single or dual antiplatelet therapy (clopidogrel or aspirin and dipyridamole). The results showed that triple antiplatelet therapy was not superior to dual therapy in reducing risks of recurrent stroke or TIA ($p = 0.47$) and increased risks of bleeding events. Therefore, combination therapy of aspirin, clopidogrel, and dipyridamole should be avoided.⁶⁴

Clopidogrel (Plavix)

Clopidogrel (Plavix) is a prodrug thienopyridine derivative platelet aggregation inhibitor that interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. Indications for clopidogrel include the reduction of atherosclerotic events in patients with a history of MI, stroke, or peripheral arteriolar disease and acute coronary syndrome (ACS) regardless of whether a patient is managed medically, by percutaneous coronary intervention (PCI), or by coronary artery bypass grafting. Clopidogrel is slightly more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic vascular disease.⁶⁵ For patients with ACS, clopidogrel plus aspirin was found to be superior to aspirin alone in reducing composite endpoints of MI, stroke, and cardiovascular death. Clopidogrel has not shown superiority to aspirin for stroke prophylaxis except in patients with peripheral vascular disease.

Clopidogrel is extensively metabolized by the liver; its metabolites are eliminated equally via the kidneys and the feces. The half-life of clopidogrel metabolites is 8 hours; steady state is reached in 3 to 7 days. The onset of action of clopidogrel can be seen in 2 hours. The average platelet inhibition seen with clopidogrel is between 40% and 60%. Platelet aggregation and bleeding time return to normal within 5 days after clopidogrel discontinuation. The dose of clopidogrel in ACS is a 300-mg loading dose followed by 75 mg once daily (plus aspirin). A higher loading dose of 600 mg is recommended for patients undergoing PCI. For the prevention of cardiovascular events such as ACS, stroke, and peripheral arterial disease, the dose is 75 mg of clopidogrel once daily.

Because clopidogrel is a prodrug, it must undergo a two-step hepatic conversion to be activated. Only about 15% of the drug

is converted to its active form, mainly through CYP2C19 and CYP3A4. Several trials have evaluated the possible interactions between clopidogrel and other drugs that can inhibit or competitively bind to these same isoenzymes, potentially inhibiting the conversion of clopidogrel to its active form and rendering the drug ineffective. PPIs, which are commonly prescribed for prophylaxis of stress ulcer, gastrointestinal reflux disease, and prophylaxis of gastrointestinal bleeding, are metabolized by CYP2C19 at varying degrees. Studies have reported that there is a significant increase in clinical event rates (e.g., MI, death) or greater platelet reactivity with concurrent use of clopidogrel and a PPI. Pantoprazole (Protonix) is the only PPI that does not undergo CYP2C19 metabolism and may potentially be devoid of this interaction, but more studies need to be conducted to confirm this. Other medications such as cimetidine, etravirine, felbamate, fluconazole, fluvoxamine, fluoxetine, ketoconazole, voriconazole, and ticlopidine should also be avoided because they can reduce antiplatelet activity of clopidogrel.

Statins or reductase inhibitors have also been an area of interest with regard to clopidogrel drug interactions. Similar to clopidogrel, statins are CYP3A4 substrates. In vivo studies that examined the degree of platelet inhibition by clopidogrel in patients taking a statin have shown that there is a significant decline in platelet inhibition with the use of statins. However, no large clinical trials have shown that this interaction can lead to negative clinical outcomes. Despite the lack of clinical trials evaluating the interaction between statins and clopidogrel, caution is advised when combining these two medications. If statin therapy is required, pravastatin (Pravachol) or rosuvastatin (Crestor) should be considered because these drugs do not undergo CYP3A4 metabolism and potentially are devoid of any significant drug interactions.⁶⁶

Testing for genetic polymorphism has also received considerable emphasis in the FDA boxed warning for clopidogrel. Although genetic polymorphism for CYP2C19 has been shown in several studies to reduce antiplatelet activity and increase major adverse cardiac events (MACEs), prospective studies show clinical efficacy of personalizing antiplatelet therapy based on genotype analysis. The recommendation issued by the FDA to clinicians is to consider alternative treatment strategies, such as combining clopidogrel with cilostazol or using high-dose clopidogrel (600 mg loading dose followed by 150 mg daily for ACS) in patients identified as poor CYP2C19 metabolizers.

Unrelated to genetic polymorphisms and clopidogrel resistance, a study of 25,086 patients evaluated the dose of clopidogrel plus the dose of aspirin for patients with ACS and those undergoing PCI.⁶⁷ There was no difference in the primary endpoint of CV death, MI, or stroke at 30 days between the double-dose clopidogrel (600 mg on day 1, followed by 150 mg for 6 days, then 75 mg daily) versus a standard-dose clopidogrel 75 mg daily with either low-dose or high-dose aspirin. The secondary endpoint of definite stent thrombosis in those undergoing PCI was reduced in the clopidogrel higher-dose group for both drug eluting stent (DES) versus non-DES subtypes, but this benefit was offset by increased major bleeding in the higher-dose clopidogrel group. The efficacy and safety of these approaches remain uncertain and more studies are necessary.⁶⁷ Alternatively, one may consider switching to another antiplatelet agent, such as prasugrel or ticagrelor, which does not undergo CYP2C19 metabolism.

The most common adverse effect of clopidogrel is hemorrhage, manifesting with purpura and epistaxis; other adverse effects include headaches, dizziness, abdominal pain, diarrhea, rash, and pruritus. In contrast to ticlopidine, clopidogrel has a lower

incidence of rash, gastrointestinal disturbances, neutropenia, and thrombotic thrombocytopenic purpura (TTP), and cholestatic jaundice has not been reported with clopidogrel.

Ticlopidine (Ticlid)

Ticlopidine (Ticlid), a thienopyridine, is a platelet aggregation inhibitor that interferes with platelet membrane function by inhibiting ADP-induced platelet–fibrinogen binding and subsequent platelet–platelet interactions. The effect of ticlopidine on platelet function is irreversible and lasts for the life of the platelet. Ticlopidine was indicated for stroke prevention. In the Ticlopidine Aspirin Stroke Study (TASS), the ticlopidine group had a 21% greater relative risk reduction for stroke compared with the aspirin group and a 9% greater reduction in stroke, MI, or vascular death at 3 years.⁶⁸ The Canadian-American Ticlopidine Study (CATS) showed that ticlopidine reduced the relative risk of stroke, MI, or vascular death by 30% compared with a placebo (10.8%; $P = .006$).⁶⁹ The half-life of ticlopidine is 14 hours; however, with repeat doses it approaches 4 to 5 days. Steady state is achieved within 14 to 21 days. Platelet aggregation is inhibited 50% within 4 days and 60% to 70% within 10 days. Platelet aggregation and bleeding time return to normal within 14 days after ticlopidine discontinuation. Ticlopidine is extensively metabolized by the liver; active metabolites have not been elucidated. At this time, ticlopidine is no longer available on the US market.⁷⁰

Prasugrel (Effient)

Prasugrel (Effient) is a prodrug thienopyridine-derivative platelet aggregation inhibitor that interferes with platelet membrane function by inhibiting ADP-induced platelet–fibrinogen binding and subsequent platelet–platelet interactions. When prasugrel is compared with other agents in the same class, it has a very limited scope; it is indicated only for the prevention of thrombosis in patients with ACS undergoing PCI. Prasugrel in combination with aspirin decreases nonfatal MI slightly more than clopidogrel in combination with aspirin but with an increased risk of bleeding. Prasugrel is contraindicated in patients who have had history of a TIA or stroke. In patients older than 75 years or in patients who weigh less than 60 kg, prasugrel was shown to have a greater risk of bleeding, which outweighs its benefit.⁷¹ Prasugrel is extensively metabolized by hydrolysis in the liver followed by CYP3A4 and CYP2D6; its metabolites are eliminated via the kidneys and feces. The half-life of the active metabolite of prasugrel is 7 to 8 hours. The onset of action of prasugrel can be seen in 30 minutes. The average platelet inhibition observed with prasugrel is 50% to 80%. Platelet aggregation and bleeding time return to normal approximately 5 to 9 days after prasugrel discontinuation. The dose of prasugrel in ACS is a 60-mg loading dose followed by 10 mg once daily (plus aspirin). In patients who weigh less than 60 kg, a decreased dose of 5 mg is recommended, although there have not been any clinical trials to support this practice.

The most common adverse effect of prasugrel is hemorrhage, which is greater than that observed with clopidogrel. Other adverse effects are similar to clopidogrel. A higher incidence of colonic neoplasm was seen during the trial for its approval.^{71,72}

Ticagrelor (Brilinta)

Ticagrelor (Brilinta) is a reversible and noncompetitive inhibitor of the ADP P2Y₁₂ receptor on the platelet surface.⁷³ It prevents ADP-mediated activation of the GPIIb/IIIa receptor complex, resulting in decreased platelet aggregation. Ticagrelor is indicated to reduce the rate of thrombotic cardiovascular events in patients

with ACS and the rate of stent thrombosis in patients treated with PCI and for acute ischemic stroke. For management of ACS, ticagrelor has been shown to decrease the combined rate of cardiovascular death, MI, and stroke compared with clopidogrel, though no difference in rate of stroke was evident. However, ticagrelor has been associated with increased noncoronary artery bypass graft (CABG)-related bleeding and discontinuation caused by adverse effects compared with clopidogrel.^{73,74} Similarly, prasugrel has also been shown to reduce the combined rate of cardiovascular death, nonfatal MI, and nonfatal stroke compared with clopidogrel, but it too has an increased bleeding risk.^{72,74} Although there is a plethora of data comparing ticagrelor or prasugrel to clopidogrel, there is a dearth of data regarding the efficacy and safety of ticagrelor compared with prasugrel.²² When ticagrelor is used, it should be initiated with a loading dose of 180 mg and continued with a dose of 90 mg twice daily. Patients with acute ischemic stroke should be taking ticagrelor for up to 30 days, while those with ACS should be taking it for a minimum of 1 year. After 1 year, dose should be lowered to 60 mg twice daily. Ticagrelor should be used together with an initial loading dose of aspirin 325 mg followed by aspirin 75 to 100 mg daily. Most significant adverse effect is hemorrhage and dyspnea and its use is contraindicated in patients with active pathological bleeding and a history of intracranial hemorrhage; it should also not be used in patients with severe hepatic impairment or hypersensitivity to ticagrelor or any of its components. The risk for bleeding with ticagrelor is increased in patients with a recent trauma or surgery, recent gastrointestinal bleeding, peptic ulcer disease, moderate to severe hepatic impairment, surgical procedure, advanced age, or concomitant use of drugs that increase bleeding risk, including anticoagulants, antiplatelets, NSAIDs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. Other adverse effects that may occur with ticagrelor use include dyspnea, headache, bradyarrhythmias, and increased serum creatinine. Ticagrelor is a CYP3A4 substrate and should not be used together with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, nelfinavir, saquinavir, or indinavir; this may increase the serum concentration of ticagrelor. It should also not be used with strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort, and phenytoin, which may decrease the serum concentration of ticagrelor. Additionally, although ticagrelor is used together with aspirin, aspirin maintenance doses greater than 100 mg reduce the effectiveness of ticagrelor and should be avoided.^{73,74}

Cangrelor (Kangreal)

Cangrelor (Kangreal) is a nonthienopyridine P2Y₁₂ receptor antagonist that selectively and reversibly binds to platelets and prevents further activation of platelets at the GPIIb/IIIa receptor. Cangrelor is indicated as adjunct to PCI to reduce the risks of periprocedural MI, recurrent coronary revascularization, and stent thrombosis in patients who have not received a P2Y₁₂ inhibitor before and are not given GPIIb/IIIa inhibitor, and is unique in that it is the first oral P2Y₁₂ inhibitor available. Cangrelor was compared to clopidogrel in three clinical trials: CHAMPION-PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX. In the trials, cangrelor infusion was compared to 600 mg of clopidogrel loading dose given before PCI, 600 mg of clopidogrel loading dose given after PCI, or 300 mg or 600 mg of clopidogrel loading dose given shortly before or after PCI, respectively. Only the CHAMPION PHOENIX trial (cangrelor versus 300 or 600 mg of clopidogrel loading) showed that cangrelor significantly reduced

risks of primary endpoint (composite of death due to any cause, MI, revascularization, or stent thrombosis), and was not associated with increased risks of major bleeding or minor events.^{75,76} Cangrelor is to be administered as a 30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV continuous infusion for a minimum of 2 hours or for the entire duration of PCI, whichever takes longer. To transition to an oral P2Y₁₂ inhibitor, loading dose of clopidogrel (600 mg) or prasugrel (60 mg) should be given immediately after termination of cangrelor infusion, while ticagrelor (180 mg) can be given during infusion or immediately after infusion. Maximal serum concentration is achieved within 2 minutes after IV bolus and infusion are initiated. Cangrelor is 97 to 98% protein bound and is not metabolized by CYP enzymes. It has a short half-life of 3 to 6 minutes and is eliminated in the urine (58%) and feces (35%).⁷⁶

Due to its short half-life, cangrelor has an advantage over the other P2Y₁₂ inhibitors as it can be discontinued right before cardiac surgery, rather than having to be held 5 to 7 days prior. In the BRIDGE trial, cangrelor 0.75 mcg/kg/min significantly reduced levels of platelet reactivity as compared to the placebo group prior to cardiac surgery. Bleeding rates were comparable between cangrelor and placebo.⁷⁶ As the BRIDGE study did not investigate clinical efficacy endpoints (e.g. MI, death due to cardiac causes), the role of cangrelor as a bridge therapy to surgery from oral P2Y₁₂ inhibitors remains unclear. Cangrelor can reduce the antiplatelet effect of clopidogrel or prasugrel, and therefore, clopidogrel or prasugrel must be initiated after completion of cangrelor infusion.⁷⁶

Cilostazol (Pletal) and Pentoxifylline (Trental)

Cilostazol (Pletal) is a quinolinone derivative that selectively and reversibly inhibits cellular phosphodiesterase III by increasing the levels of cAMP, resulting in vasodilation and inhibition of platelet aggregation. Cilostazol is indicated for intermittent claudication in patients with peripheral arterial disease. Cilostazol allows for increased walking distances and improves symptoms and quality of life in patients with intermittent claudication. The clinical benefits may not be noticed for at least 2 to 4 weeks and may take 12 weeks. The only alternative to cilostazol for intermittent claudication is pentoxifylline (Trental); however, it has been proven ineffective. Pentoxifylline is a xanthine agent with rheologic properties that decrease blood viscosity and improve erythrocyte flexibility.

Cilostazol is associated with a high incidence of transient adverse effects, such as headache, diarrhea, dizziness, and palpitations. In patients with heart failure, oral phosphodiesterase inhibitors such as milrinone have been associated with increased mortality resulting from arrhythmias; cilostazol and several of its metabolites are contraindicated in patients with heart failure and should be used prudently in patients with CAD. Cilostazol has been associated with increases in heart rate and reductions in P–R, QRS, and Q–T intervals on ECG. In the dog model, cilostazol has been associated with cardiac lesions and endocardial hemorrhage, similar to toxicities noted with milrinone; the risk of developing cardiac lesions with long-term cilostazol use is unknown. Cilostazol is a CYP3A4 and CYP2C19 substrate and has been associated with significantly elevated levels when combined with the CYP3A4 inhibitors ketoconazole, diltiazem, and erythromycin. Smokers exhibited 20% lower levels of cilostazol. Cilostazol is administered at 100 mg twice daily; the dose should be reduced in the presence of CYP3A4 inhibitors to 50 mg twice daily. Food increases the bioavailability of cilostazol by 90%; cilostazol should be administered on an

empty stomach to circumvent this interaction. Grapefruit juice inhibits gut CYP3A4 and may increase plasma cilostazol levels and should be avoided during cilostazol use.

Vorapaxar (Zontivity)

Vorapaxar (Zontivity) is the only protease-activated receptor-1 (PAR-1) antagonist currently on the market. Vorapaxar inhibits PAR-1 on the platelet surface, resulting in inhibition of thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation.⁷⁷ Although its antiplatelet activity is reversible, because of its prolonged half-life it is effectively irreversible. Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with peripheral arterial disease or a history of MI.⁷⁷ Vorapaxar has been shown to decrease the combined rate of cardiovascular death, MI, stroke, and urgent coronary revascularization. Vorapaxar is given at a dose of 2.08 mg once daily together with aspirin and/or clopidogrel. Vorapaxar should generally not be used as the sole antiplatelet agent or with other antiplatelet agents besides aspirin and clopidogrel because of limited data regarding efficacy and safety. Because of risk for bleeding with vorapaxar, use is contraindicated in patients with active pathological bleeding or a history of stroke, transient ischemic attack, or intracranial hemorrhage. Risk for bleeding is highest in patients who are older in age, have a low body weight, have reduced renal or hepatic function, have a history of bleeding disorders, or are using vorapaxar together with other drugs that increase bleeding risk, including anticoagulants, antiplatelets, NSAIDs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. Vorapaxar is a substrate of CYP3A4 and CYP2J2. Vorapaxar should not be used together with strong CYP3A4 inhibitors, which may increase the serum concentration of vorapaxar, or with strong CYP3A4 inducers, which may decrease the serum concentration of vorapaxar.⁷⁷

Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors are indicated for the treatment of patients with ACS—unstable angina or non-ST segment elevation acute MI—and patients who are medically managed and patients undergoing PCI. Abciximab (ReoPro) is the GP IIb/IIIa inhibitor of choice for PCI. The management of unstable angina or non-ST segment elevation acute MI includes the use of aspirin, heparin, and a GP IIb/IIIa inhibitor. This combination has led to a decrease in the composite endpoints of new MI or death.⁷⁸ In patients who are being managed medically for a non-ST segment elevation ACS, the use of GP IIb/IIIa inhibitors has been marginalized to patients with moderate to high risk based on a risk assessment score and continued ischemia or patients with diabetes. GP IIb/IIIa inhibitors are administered via continuous intravenous infusions.⁷⁸ Oral formulations of GP IIb/IIIa inhibitors failed to display efficacy in clinical trials and are unavailable.

The most common adverse effect reported during therapy was bleeding. The incidence of major bleeding manifesting as gastrointestinal, genitourinary, or intracranial hemorrhage with the three-drug combination was only slightly greater than with aspirin and heparin alone, illustrating the safety of the GP IIb/IIIa inhibitors. Although minor bleeding with GP IIb/IIIa inhibitors is common (10%), it is generally inconsequential. Because these agents may cause thrombocytopenia, monitoring of the daily platelet, hemoglobin, and hematocrit is required. Abciximab has been implicated as a cause of immune-mediated thrombocytopenia in 5% of patients. Table 22.20 presents the pharmacologic characteristics of GP IIb/IIIa inhibitors.

TABLE 22.20 Characteristics of Glycoprotein IIb/IIIa Inhibitors

	Abciximab	Tirofiban	Eptifibatide
Brand name	Reopro	Aggrastat	Integrilin
Common uses	Adjunct to PCI	Management of ACS, medically or with PCI	Management of ACS, medically or with PCI; adjunct to PCI
Pharmacology	Chimeric human-murine monoclonal antibody Fab fragment GP IIb/IIIa inhibitor	Nonpeptide GP IIb/IIIa inhibitor	Cyclic heptapeptide GP IIb/IIIa inhibitor
Origin	Antibodies from immunized mice	Chemically derived	Active component of snake venom peptides
Binding to platelets	Irreversible	Reversible	Reversible
Elimination half-life	30 min	2 hr	2.5 hr
Platelet function recovery	Approximately 48 hr	Approximately 4 hr	Approximately 4 hr
Elimination	Renal, lymphatic system	65% renal, 25% biliary	50% renal, 30% metabolized in plasma into amino acids

ACS, Acute coronary syndrome; PCI, percutaneous coronary intervention.

Thrombolytic Agents

Thrombolytics are indicated for the management of PE, ischemic stroke, and acute ST segment elevation MI—the most extensive and life-threatening type of heart attack. Thrombolytics reduce the incidence of heart failure and death associated with acute MI and restore coronary blood flow by dissolving the thrombus, limiting the extent of ischemia and necrosis. Thrombolytics convert plasminogen to plasmin. Subsequently, the proteolytic enzyme plasmin initiates clot lysis and produces FDPs.

For the treatment of ST segment elevation ACS manifesting with at least 1 mm of ST segment elevation in two or more contiguous ECG leads, all available thrombolytics (alteplase, reteplase, and tenecteplase) are indicated. Eligible patients should receive thrombolytic therapy within 12 hours of symptom onset; however, a benefit can be realized for 24 hours. Thrombolytics are preferred to primary PCI when patients present within 12 hours of symptom onset and the *first medical contact to primary PCI time* would be greater than 120 minutes. For acute massive PE, alteplase is the only thrombolytic indicated. Alteplase is reserved for patients with acute massive PE who present with symptoms within 2 weeks but optimally within 5 days. Alteplase is the only thrombolytic indicated for the management of acute ischemic stroke for patients who present within 3 hours of symptom onset and no later than 4.5 hours after onset.⁷⁹ The use of thrombolytics is often precluded because of their extensive list of contraindications.⁸⁰ The absolute and relative contraindications for the use of thrombolytics are listed in [Box 22.2](#).

The most common adverse effect associated with these agents is major and minor bleeding. Major bleeding includes gastrointestinal, genitourinary, respiratory tract, retroperitoneal, and intracranial hemorrhage. Minor bleeding often manifests as superficial or surface bleeding as a result of arterial punctures and surgical intervention. Thrombolytic-induced hemorrhagic stroke in patients older than 75 years occurs more often with alteplase than with streptokinase. Alteplase and tenecteplase are known to be fibrin specific because they promote the conversion of plasminogen into plasmin in the presence of clot-bound

• BOX 22.2 Thrombolytic Contraindications in Acute Treatment of Stroke

Absolute

- History or evidence of intracranial hemorrhage
- Clinical presentation suggestive of subarachnoid hemorrhage
- Known arteriovenous malformation
- SBP greater than 185 mm Hg or DBP greater than 110 mm Hg despite repeated measurements and treatment
- Platelet count less than 100,000/mm³
- Prothrombin time greater than 15 seconds or INR greater than 1.7
- Active internal bleeding or acute trauma (fracture)
- Head trauma or stroke within previous 3 months
- Arterial puncture at noncompressible site within 1 week
- Active internal bleeding
- Concurrent use of direct thrombin inhibitors (DTIs) or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as activated partial thromboplastin time [aPTT], international normalized ratio [INR], platelet count, and ecarin clotting time [ECT]; thrombin time [TT]; or appropriate factor Xa activity assays)
- Blood glucose concentration less than 50 mg/dL (2.7 mmol/L)
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Recent intracranial or intraspinal surgery

Relative

- Rapidly improving stroke symptoms
- Myocardial infarction in the previous 3 months
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Major surgery or serious trauma within previous 14 days
- Seizure with postictal residual neurologic impairment
- Pregnancy

fibrin only, with limited systemic proteolysis. The increased fibrin specificity is believed to induce less extensive systemic depletion of clotting factors such as fibrinogen and plasminogen. The clinical relevance of thrombolytic fibrin specificity

TABLE 22.21 Pharmacologic Properties of Thrombolytic Agents

	Alteplase (rtPA)	Reteplase (rPA)	Tenecteplase (TNK-tPA)
Brand name	Activase	Retavase	TNKase
Source	Recombinant DNA technology using heterologous mammalian tissue culture	Recombinant DNA technology using <i>Escherichia coli</i>	Recombinant DNA technology using Chinese hamster ovary cells
Common uses	Pulmonary embolism, stroke, clearance of occluded central venous access device, ST segment elevation	Myocardial infarction, ST segment elevation	Myocardial infarction, ST segment elevation
Type of agent	Tissue plasminogen activator	Tissue plasminogen activator	Tissue plasminogen activator
Plasma half-life (min)	2–6	13–16	90–130
Fibrinolytic activation	Systemic	Systemic	Systemic
Antigenic	No	No	No
Fibrin specific	+++	++	++++
Systemic bleeding risk	++	++	+
ICH risk	++	++	++

ICH, Intracranial hemorrhage; rPA, recombinant plasminogen activator; rtPA, recombinant tissue-type plasminogen activator; TNK, tenecteplase; tPA, tissue-type plasminogen activator.

has not been elucidated. Thrombolytics have rarely been associated with cholesterol embolization manifesting as purple toe syndrome, livido reticularis, acute renal failure, gangrene, MI, bowel infarction, stroke, and rhabdomyolysis. When

thrombolytics are used for ACS, they can cause reperfusion arrhythmias manifesting as bradycardia or ventricular tachyarrhythmias. Table 22.21 presents the pharmacologic properties of thrombolytic agents.^{81,82}

SELF-ASSESSMENT QUESTIONS

Answers can be found in [Appendix A](#).

1. What is the systolic and diastolic blood pressure goal for patients without any comorbidities?
2. List adverse effects associated with angiotensin-converting enzyme inhibitors (ACEIs).
3. Which antihypertensive agents are preferred in the treatment of Black patients without any comorbidities?
4. Which of the β blockers possess intrinsic sympathomimetic activity (ISA)?
5. Which of the β blockers possess selective β_1 -blocker activity?
6. List adverse effects associated with α_1 -adrenergic antagonists.
7. What are the most common side effects of nitrates?
8. List metabolic effects associated with thiazide diuretics.
9. Name five medications that may cause drug-induced increases in blood pressure.
10. Which calcium channel blocker is most likely to cause constipation?
11. Identify the best available parameter to monitor the effects of warfarin.
12. What is the antidote for heparin?
13. What is the mechanism of action of warfarin?
14. List the commercially available oral factor Xa inhibitors.
15. Identify the commercially available oral direct thrombin inhibitor.
16. List the common CYP3A4 and P-glycoprotein inhibitors.
17. Name the pharmacologic class responsible for inhibiting the final pathway in platelet aggregation.
18. Which thrombolytic is preferred for massive pulmonary embolism?
19. Name the only ACEI that is available in a parenteral dosage form.
20. Identify the best available parameter to monitor the effects of heparin.
21. Is clopidogrel or ticlopidine superior to aspirin for stroke prevention?

CLINICAL SCENARIO

Answers can be found in [Appendix A](#).

A 75-year-old man presents to the emergency department complaining of chest pain of 1 hour in duration. He has had intermittent chest pain for the past week. He describes experiencing substernal pain that radiates down his left arm. The pain is associated with diaphoresis and is not relieved by change in body position. He has had a history of hypertension for the past 10 years. He has no history or family history of coronary artery disease. He is currently taking labetalol, 200 mg twice daily, and an enteric-coated aspirin, 81 mg daily. He has no known allergies.

On physical examination, he appears anxious and is complaining of chest pain. His vital signs are as follows: blood pressure (BP) of 140/70 mm Hg, pulse (P) of 74 beats/min, and respiratory rate (RR) of 20 breaths/min. His heart sounds are normal, with no murmurs or gallops present. His lungs are clear on auscultation, and his abdomen, extremities, and fundoscopic examination are unremarkable. His skin is cool and clammy.

Electrocardiography (ECG) shows evidence of sinus bradycardia with a heart rate of 49 beats/min. His cardiac enzymes all are elevated (creatinine kinase [CK] of 200 U/L, CK-MB [CK isoenzymes found in muscle and brain fractions] of 20 U/L, and troponin I of 2 mcg/mL).

Based on his history, physical examination, and ECG, this 75-year-old man is diagnosed with non-ST segment elevation myocardial infarction (MI).

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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23

Sleep and Sleep Pharmacology

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CHAPTER OUTLINE

History of Treatment of Sleep Disorders

Progression of Sleep

Neurophysiologic Mechanisms

Arousal and Wakefulness

Ascending Reticular Activating System

Thalamic Mechanisms of Arousal

Sleep Onset and Processes That Maintain Sleep

Two-Process Model of Sleep Regulation

Circadian Processes and Chronobiology

Circadian Timing System

Suprachiasmatic Nucleus: The Central Oscillator

Circadian Rhythm and Metabolism

Chronopharmacology

Melatonin as a Chronobiotic and Chronohypnotic Agent

Sleep Disorders: Causes and Treatments

Insomnia

Restless Legs Syndrome and Periodic Limb Movement Disorder

Narcolepsy

Parasomnias

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to sleep and sleep pharmacology
2. Describe sleep, its individual stages, and their electrophysiologic correlates
3. Comprehend the basic neurophysiologic mechanisms that promote brain arousal and wakefulness
4. Comprehend the basic neurophysiologic mechanisms that promote sleep onset and maintenance
5. Describe basic circadian processes and their interaction with the sleep–wake cycle
6. Recognize several sleep disorders that are amenable to pharmacotherapy
7. Describe the rationale for using certain classes of drugs to treat specific sleep-related disorders

KEY TERMS AND DEFINITIONS

Barbiturates Compounds whose parent structure is uric acid.

These compounds depress central nervous system activity. Long-acting barbiturates such as pentobarbital have been used to treat epilepsy. Barbital was used during the early 20th century to facilitate sleep in individuals with insomnia.

Benzodiazepines Compounds whose parent structure is a fusion of a diazepine ring with a benzene ring. Benzodiazepines enhance the activity of the inhibitory neurotransmitter γ -aminobutyric acid (GABA). Benzodiazepines, which reduce anxiety and promote muscle relaxation, also promote sleep. The earliest benzodiazepines were chlorthalidoxepoxide (Librium) and diazepam (Valium). Benzodiazepines for insomnia are now being replaced by nonbenzodiazepines such as zolpidem (Ambien), eszopiclone (Lunesta), and others.

Circadian rhythms “Circa” is Latin for “about,” and “diem” is Latin for “day.” Circadian rhythms refer to the approximately 24-hour cycle of biochemical, physiologic, and behavioral processes.

Electroencephalography (EEG) Measurement and recording of the gross electrical activity of the brain. During EEG recordings, electrodes are typically placed across multiple scalp regions. The

electrodes are connected to amplifiers and filters that detect, magnify, and record the electrical activity of the brain.

Hypersomnolence Refers to the symptom of excessive sleepiness. Daytime sleepiness is so great that it leads to inappropriate daytime napping or sleep.

Hypersomnia Indicates specific disorders, such as idiopathic hypersomnia. Excessive sleepiness is not alleviated by prolonged sleep times or by napping.

Hypnotic Class of drugs used to induce sleep.

Nycthemeron A period of 24 consecutive hours consisting of day and night

Parasomnia The *International Classification of Sleep Disorders, 3rd Edition (ICSD-3)* defines parasomnia as “undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. Parasomnias may occur during non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), or during transitions to and from sleep.”

More commonly encountered parasomnias include confusional arousals, sleep terrors, sleepwalking, and nightmares.

Polysomnography Measurement and recording of EEG activity, typically coupled with measurement and recording of cardiorespiratory activity and eye movements, during sleep.

Smith-Magenis Syndrome (SMS) A rare genetic disorder that is caused by a small deletion of human chromosome 17p. It

manifests with physical, mental, and behavioral problems, and a prominent feature of it is a severe sleep disorder combined with considerable disruption in the lives of patients and their families.

History of Treatment of Sleep Disorders

The origins of sleep and the meaning of dreams have fascinated people for centuries—from philosophers to poets, ideas of the significance of sleep abound. Edgar Allen Poe described sleep as “little slices of death,” whereas William Shakespeare regarded it to be the “chief nourisher in life’s feast.” Until more recently, sleep was considered to be a passive, dormant counterpart to waking life. We now know that sleep is an active process that may look similar to but is very different from anesthesia or coma.

Humans spend about a third of their lives sleeping. Sleep disorders, which affect a large proportion of the general population and occur in all age groups, represent a major public health and global economic burden.¹ It is estimated that 50 million to 70 million adults in the United States have a chronic sleep disorder that interferes with their daily functioning and adversely affects their health and quality of life. Until the mid-1960s, the field of sleep medicine focused primarily on describing and treating insomnia, parasomnias (e.g., sleepwalking, night terrors), and **hypersomnias**, such as narcolepsy. Patients experiencing these symptoms typically sought consultations from neurologists, psychiatrists, psychologists, or their family physicians. Until more recently, treatments were generally based on empiric pharmaceutical intervention and behavioral modification protocols or psychotherapy or both.

The role of the respiratory therapist in sleep medicine is still emerging, and areas of necessary proficiency and expertise are yet to be fully defined. An authoritative knowledge about sleep, sleep disorders, pharmacology, and the therapeutic actions of drugs on sleep architecture is required, together with knowledge of associated side effects or adverse drug reactions and toxicities. In the future, respiratory therapists may be involved with the attending physician in determining appropriate pharmacotherapy for sleep-related disorders, such as narcolepsy or periodic limb movement disorder (PLMD). At a minimum, it is highly probable that during sleep diagnostic procedures, the respiratory therapist will assess the patient’s current therapeutic regimen and, after consultation with the physician, determine whether medications should be temporarily suspended before diagnostic procedures. This chapter provides basic knowledge about sleep medicine for both the respiratory therapist who is still developing clinical skills and the experienced therapist who is actively participating in patient care with physicians.

KEY POINT

The most recent version of the *International Classification of Sleep Disorders, 3rd Edition (ICSD-3)*, published in 2014 by the American Academy of Sleep Medicine (AASM), classifies sleep disorders and diagnostic criteria. Diagnostic codes for each disorder are also provided. Currently, more than 60 sleep disorders are described in the ICSD-3 (Table 23.1).²

It is beyond the scope of this chapter to address the entire spectrum of sleep disorders classified in the *International Classification of Sleep Disorders, 3rd Edition (ICSD-3)* or to provide an exhaustive summary of all the pharmacologic, nutraceutical, or cognitive behavioral therapies employed in this field. This chapter describes the classes of drugs that are likely to be encountered when treating

TABLE
23.1

ICSD-3 Major Diagnostic Sections

Section

Insomnia

Sleep-related breathing disorders

Circadian rhythm sleep–wake disorders

Parasomnias

Sleep-related movement disorders

Other sleep disorders

ICSD-3, International Classification of Sleep Disorders, 3rd edition.

patients with sleep disorders. First, a broad but brief overview of the history and evolution of sleep research and sleep pharmacology is presented, followed by a brief overview of the brain mechanisms underlying the processes of wakefulness and sleep, including circadian aspects. Some key sleep-related disorders are described, and typical compounds that may be used to treat those disorders are reviewed. Adult sleep apnea syndrome, which is primarily treated with mechanical devices such as oral appliances or application of continuous positive airway pressure (CPAP), is not discussed. Apnea and bradycardia of prematurity, which is treated primarily with respiratory stimulants, are discussed in Chapter 17.

The onset and duration of sleep are orchestrated through multiple brain structures and neurotransmitter substrates, and pathology within those structures or neurotransmitter systems become manifest as a sleep disorder. For example, loss of orexin/hypocretin-producing neurons in the lateral hypothalamus is associated with the inability to maintain prolonged periods of wakefulness or sleep and the intrusion of rapid eye movement (REM) sleep, or the signs of REM sleep, into wakefulness. Sleep pharmacotherapeutics evolved with the understanding that normalization of activity within perturbed brain regions or neurotransmitter systems, or both, leads to a reduction of the signs and symptoms of specific sleep disorders.

KEY POINT

Compounds to induce and sustain sleep have been in use for almost 5000 years. The oldest may be opium (which contains morphine), whereas the most recent are orexin receptor antagonist hypnotics.

As a result of increased public awareness about sleep disorders and scientific advances, sales of sleep-related drugs have increased markedly. According to a market report published by the Persistence Market Research, “Global Market Study on Sleep Aids: Sleep Apnea to Witness Highest Growth by 2020,” the global sleep aids market was valued at US\$ 58.1 billion in 2014 and is expected to expand at a compound annual growth rate of 5.7% to account for US\$80.8 billion by 2020.³

However, the interest in pharmaceutical sleep aids is not new; sleep-inducing compounds were discovered and used thousands of years ago. Perhaps the first compound to be used as a sleep-inducing aid was the juice from the opium poppy. Some of the earliest written descriptions of the opium poppy have been found on Sumerian clay tablets dating to approximately 3000 BC. At that

time, the juice of the poppy was harvested and consumed because of its ability to induce a euphoric state; this led to the plant being considered a Gil Hul, or “joy plant.” Descriptions of the opium poppy have also appeared in writings of the Assyrians and Persians. The Greeks eventually were introduced to the opium poppy, which may represent the first time it was used expressly for sleep induction. Greek mythology depicts many sleep-related deities, including Hypnos (sleep), Morpheus (dreams), Nyx (night), and Thanatos (death, the twin brother of Hypnos), in association with opium extracted from the poppy. Homer described the properties of opium in both *The Iliad* and *The Odyssey* as an intoxicating, pain-relieving, and sleep-inducing substance.

More recent literature also expounds on the sleep-inducing power of opium in *The Wizard of Oz* with Dorothy, her dog Toto, and the Cowardly Lion falling into a deep sleep as they passed through a field of poppies on their approach to the Emerald City. The sleep-inducing effects of the opium poppy can be attributed to numerous alkaloids contained within the plant, including morphine and codeine. Both are central nervous system (CNS) depressants and opioid pain relievers.

The development of sleep-inducing compounds was revolutionized in the early 19th century by the synthesis of opium. Shortly after this, chloral hydrate and the bromides were developed. Chloral hydrate, a CNS depressant, rapidly induces deep sleep. Bromides, invented in the mid-19th century, are also CNS depressants and induce sleep relatively quickly. Their popularity as sleep aids increased through the late 19th century and into the early 20th century. Also, during the 19th century, nitrous oxide was rediscovered, and ether and nitrous oxide were inhaled as “party favorites” of upper-class Europeans and Americans. The initial discoveries of ether by the Spanish alchemist Lullius in 1275 and nitrous oxide by the English chemist Priestly in 1772 were lost to medical science until their reintroduction in 1842. At that time, Long, a surgeon in Georgia, employed the recreational drug ether in surgical procedures because of its incredibly rapid induction of “sleep, amnesia and pain relief.” In doing so, he unknowingly ushered in the modern era of anesthesia.

Barbiturates, first discovered in the mid-19th century, soon replaced bromides as the “sleeping pills” of choice in the early 20th century. This class of drugs comprises more than 25,000 compounds that were synthesized by combining various compounds with barbituric acid. Although multiple barbituric acid compounds were developed, only a select few (including a diethyl derivative) resulted in sleep-promoting properties. Barbiturates, such as phenobarbital, are very effective at inducing sleep. However, they also have multiple side effects, not the least of which is the potential risk for barbiturate addiction, and, if taken with alcohol, they can result in respiratory suppression and death. These hypnotic agents have been replaced by newer, more effective, and safer compounds.

Benzodiazepines, such as diazepam (Valium), temazepam (Restoril), and clonazepam (Klonopin) were first marketed in the 1970s. Early formulations of these CNS depressants shared similar side-effect profiles to the barbiturates, although their margin of safety was much greater. However, benzodiazepines possess the potential for addiction, and because of the long half-life and the duration needed to eliminate some benzodiazepines from the body (more than 12 to 24 hours), next-day “hangover” sleepiness effects and memory impairments are common. Since the introduction in the 1990s of nonbenzodiazepine and analogs of these compounds (e.g., zopiclone, zolpidem, zaleplon, and eszopiclone), the use of benzodiazepines for insomnia has declined.

The “ideal **hypnotic**” should possess the following principal characteristics. It should induce sleep rapidly (in about 10 to 15 minutes); maintain sleep over prolonged periods (about 7 to 8

hours); and be devoid of daytime residual side effects on memory, cognition, or alertness. It should also possess additional characteristics such as rapid absorption, optimal half-life, receptor-specific binding, no active metabolite, no potential for abuse, tolerance, or dependence, no respiratory depressive effect, and no interaction with alcohol or other CNS depressants.

In addition to “sleeping pills,” many nondepressant medications are used in sleep medicine. In disorders such as restless legs syndrome (RLS) and PLMD, sleep onset is often delayed and fragmented. First-line therapy for these disorders includes dopamine agonists and, in some cases, opiates. Respiratory stimulants are another class of medications sometimes employed in the treatment of sleep disorders. Medroxyprogesterone and acetazolamide have been used in an effort to enhance ventilation in patients with high altitude-induced central sleep apnea or obesity-hypoventilation syndrome. More recently, the antidepressant mirtazapine has been shown to reduce apnea severity in animal models emulating sleep apnea as well as in some patients.² An effective pharmaceutical treatment for obstructive sleep apnea does not yet exist.

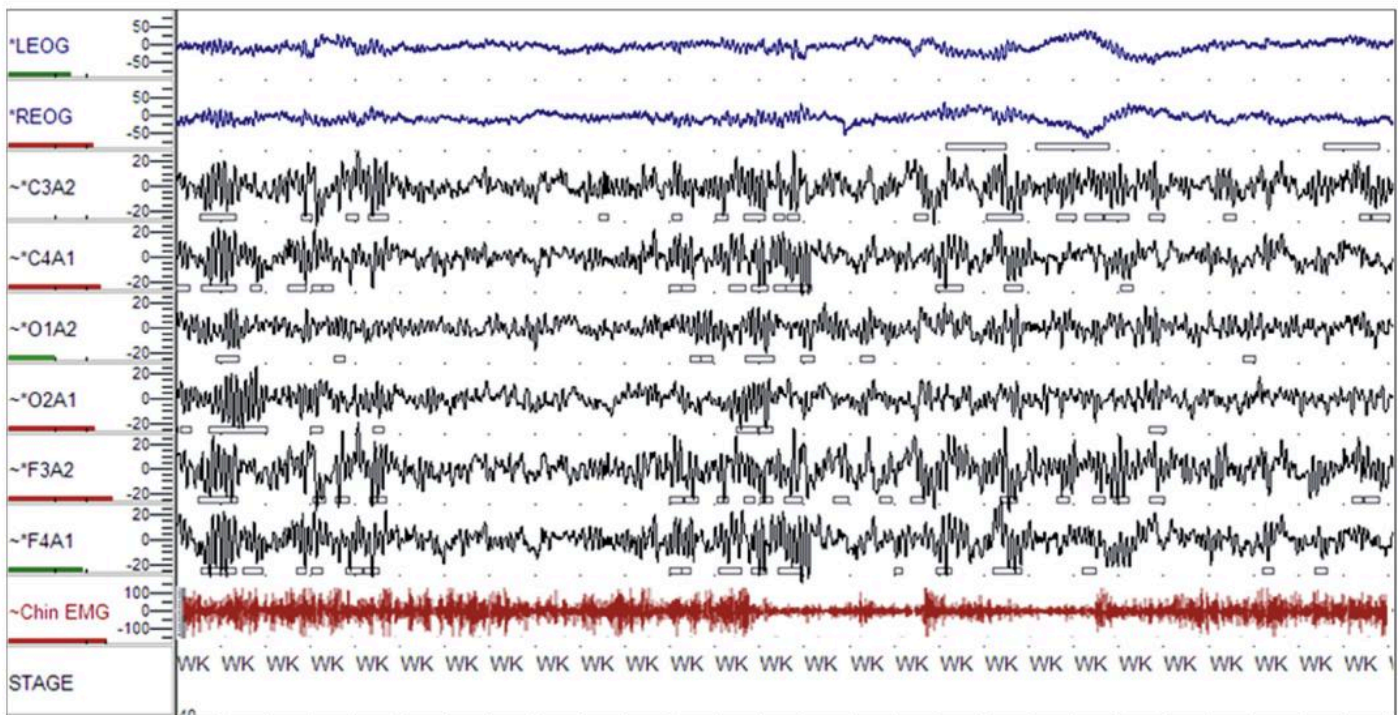
KEY POINT

Manifestations of sleep disorders can emerge from within different sleep states. REM behavior disorder occurs only during REM sleep. Confusional arousals tend to occur when awakening from slow-wave sleep (stage N3). Somnambulism (sleepwalking) is also known to occur during the first third of the night; the sleep period is predominated by slow-wave sleep (stage N3).

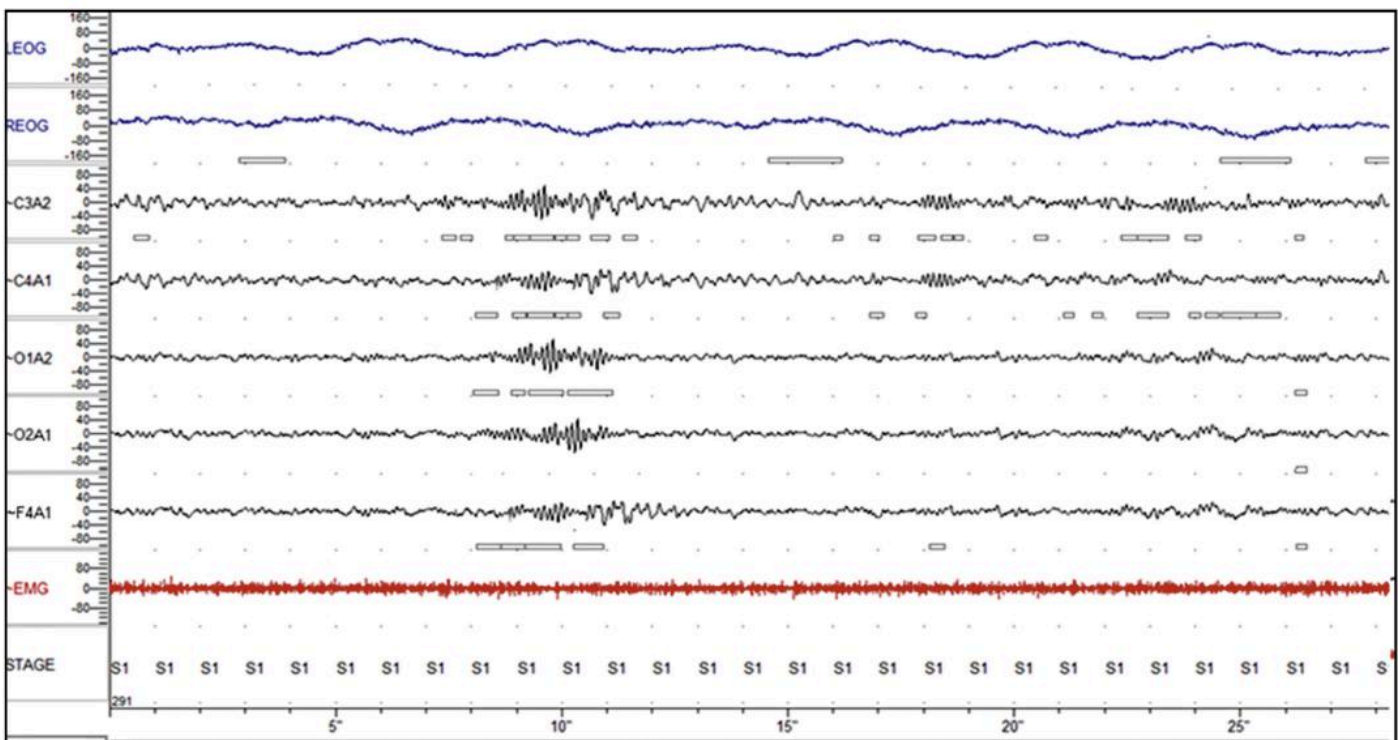
Progression of Sleep

Sleep was originally thought to be a passive rather than an active process. Richard Canton (1842–1926), a physiologist at the Royal Infirmary in Liverpool, is credited with the discovery of the electrical nature of the brain, which ultimately led to the discovery of **electroencephalography (EEG)** by Hans Berger (1873–1941), an important milestone in the understanding of human sleep as an active process. Canton’s experimental observations on cortical currents in rabbits and monkeys were published in *The British Journal of Medicine*.⁴ Using a mirror galvanometer, Canton observed an increase in the amplitude of waves measured from the cortex during states of sleep as opposed to a decrement in cortical amplitudes during wakefulness. Canton was the first to perform sleep EEG in mammals.⁵ Subsequently, several observations, including those of Constantin von Economo (1876–1931) and the experiments by Giuseppe Moruzzi (1910–1986) and Horace Winchell Magoun (1907–1991), clearly showed that sleep was not a passive phenomenon but involves several brain regions, especially the diencephalon and the brainstem, which actively control sleep and states of arousal.^{6–9} In 1957, William Charles Dement (1928–2020) and Nathaniel Kleitman (1895–1999) reported the cyclical alternating pattern of non-rapid eye movement (NREM) and REM sleep.¹⁰

When determining the most appropriate pharmaceutical intervention for a sleep disorder, it is important first to consider how sleep is defined and measured and the normative values of time spent in sleep and each sleep stage (i.e., sleep architecture). Mammalian sleep can be defined as a cyclical, reversible behavioral state of perceptual disengagement from and unresponsiveness to the external environment. Within normal human monophasic sleep, sleep is polygraphically characterized into two distinct stages based on a constellation of behavioral and electrophysiologic parameters. These two stages are NREM and REM sleep. NREM sleep is categorized further into stages N1–N3 (formerly known as stages 1 to 4); N1 is the lightest, and stage N3 is the deepest sleep stage. Figs. 23.1 to 23.4 show examples of EEG-defined wakefulness followed by examples of stages N1 to N3.



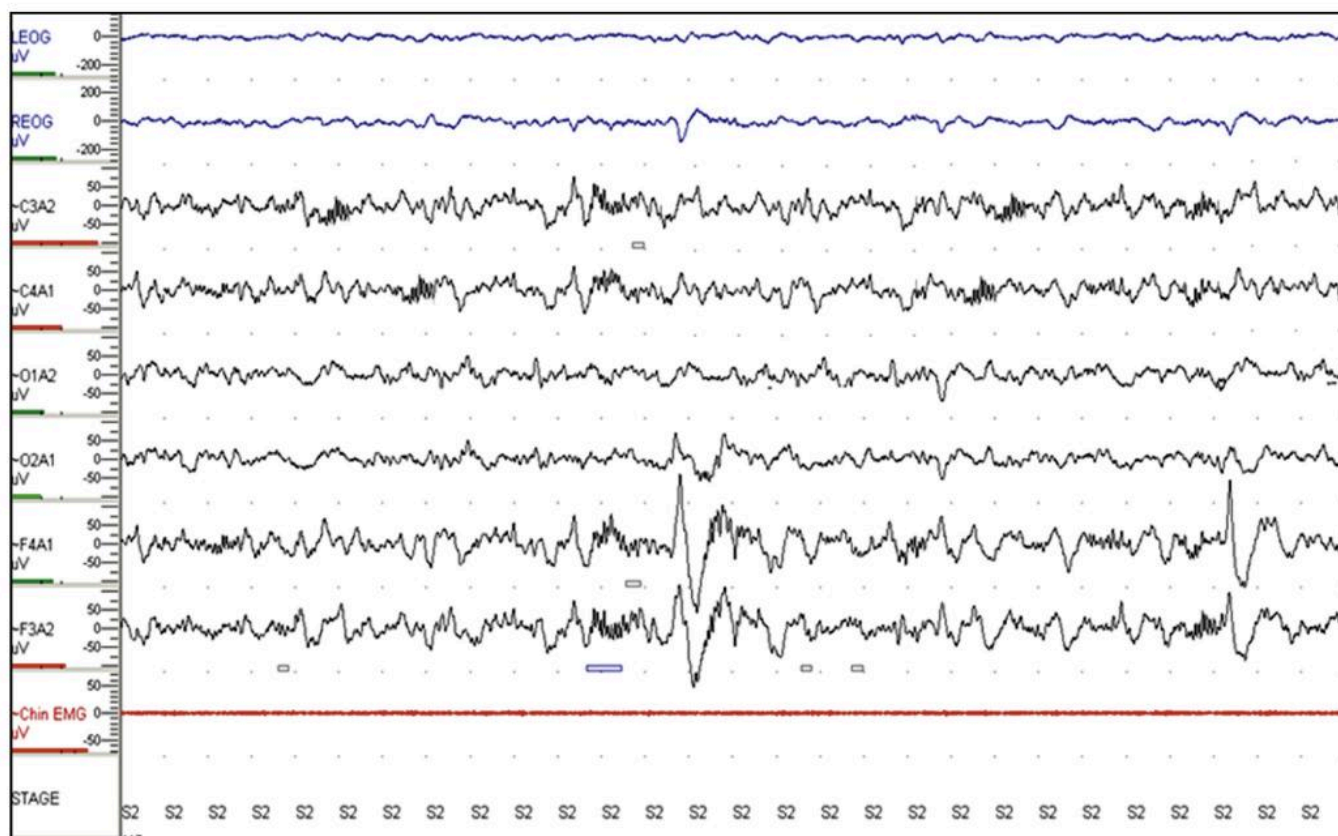
• Fig. 23.1 A 30-second epoch of wakefulness.



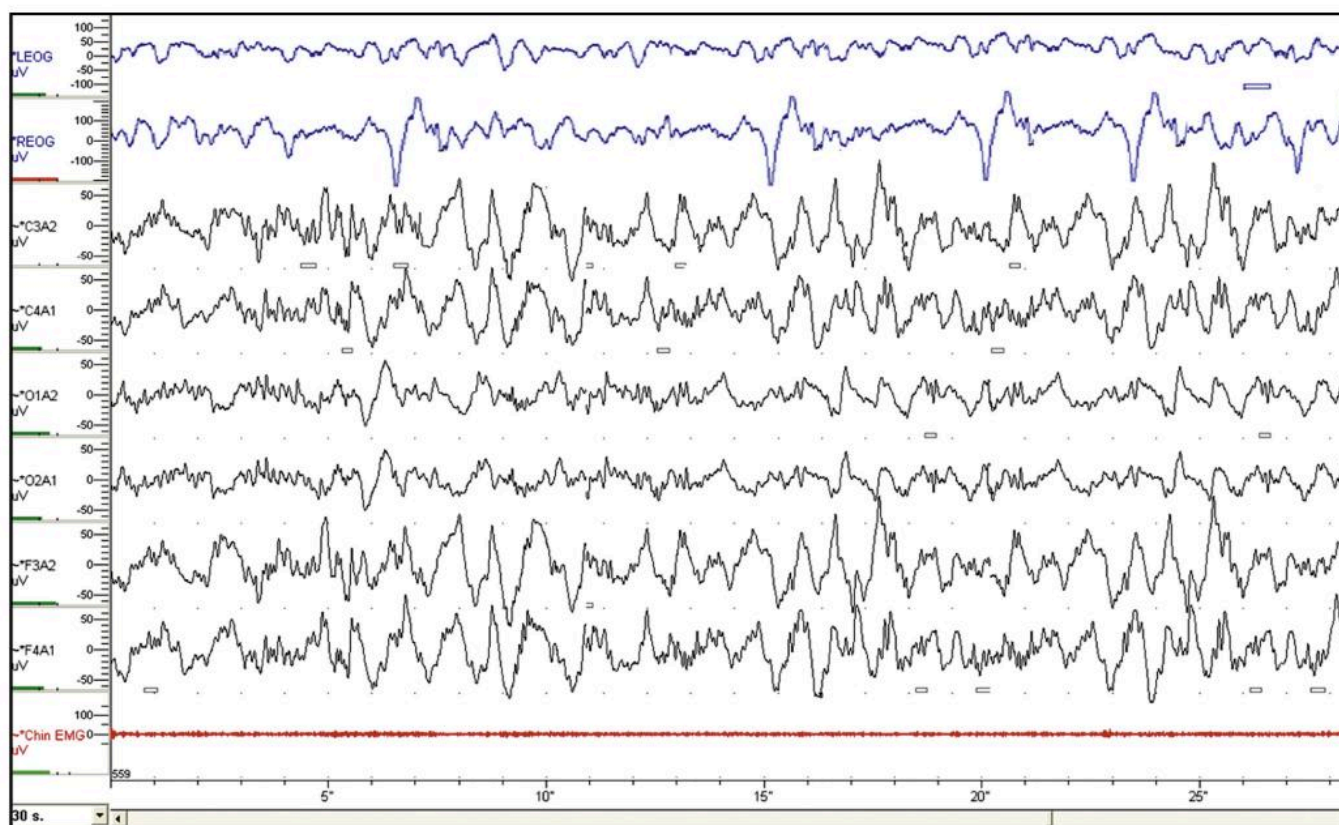
• Fig. 23.2 A 30-second epoch of sleep scored as stage N1, formerly known as stage 1.

The term for REM sleep is derived from the periodic bursts of REMs during sleep. REM sleep has both tonic (persistent) and phasic (episodic) components. During tonic REM sleep, the EEG tracing shows a similar pattern to that of N1, but it may also exhibit increased activity in the theta frequency range (3–7 Hz) and sawtooth-type waves. REM sleep is also accompanied by a generalized muscle atonia, except for the extraocular muscles and the diaphragm. Fig. 23.5 shows an example of EEG-defined REM sleep.

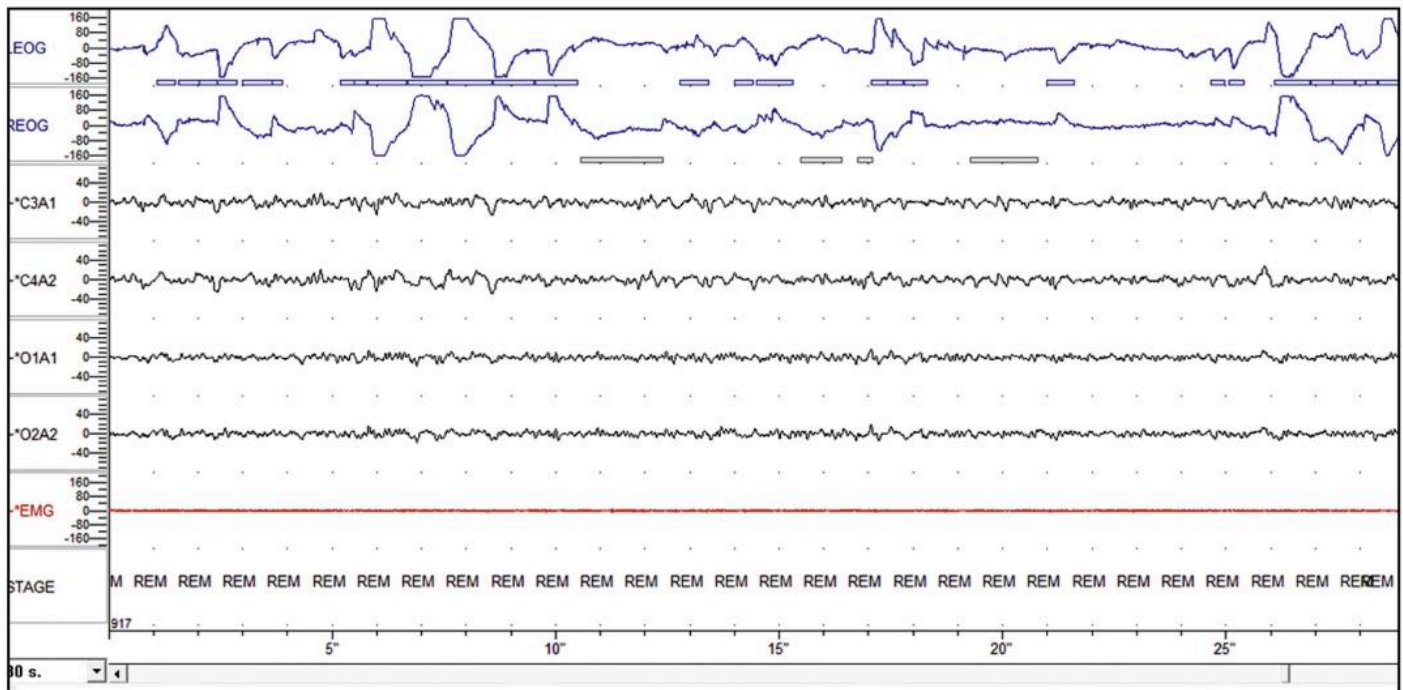
Aserinsky and Kleitman were the first to observe the electrophysiologic characteristics of REM sleep and, in particular, the rapid, jerky, and binocularly symmetric eye movements in this sleep stage.¹¹ EEG patterns similar to wakefulness were noted, showing the characteristic fast desynchronized rhythms in the cortical EEG, and the term paradoxical sleep was introduced by Michel Jouvet in 1960;¹² the term active sleep was used by other researchers. These terms are used



• **Fig. 23.3** A 30-second epoch of sleep scored as stage N2, formerly known as stage 2.



• **Fig. 23.4** A 30-second epoch of sleep scored as stage N3, formerly known as stages 3 and 4.



• **Fig. 23.5** A 30-second epoch of sleep scored as stage REM sleep.

TABLE 23.2 Electroencephalographic Correlates of Sleep Stages

Sleep Stages	TST (%)	CHARACTERISTICS			
		EEG	EOG	EMG	Other Variables
Stage awake (relaxed wakefulness)		Alpha activity (8–12 Hz) or low-amplitude beta (13–35 Hz), mixed-frequency waves	REM (in sync or out of sync deflections), eye blinks	Relatively high tonic EMG activity	Alpha activity in occipital leads compared with central leads, eye-opening suppress alpha activity, movement artifacts
N1, formerly known as stage 1	2–5	Low-voltage, mixed-frequency waves (2–7 Hz range), mainly irregular theta activity, triangular vertex waves	SEMs, waxing and waning of the alpha rhythm	Tonic EMG levels are typically below the range of relaxed wakefulness	Alpha $\leq 50\%$, vertex sharp waves in central leads, the absence of spindles and K complexes
N2, formerly known as stage 2	45–55	Relatively low-voltage, mixed-frequency waves, some low-amplitude theta and delta activity	No eye movement	Low chin muscle activity	Sleep spindles (7–14 Hz) and K-complexes occur intermittently
N3, formerly known as stages 3 and 4	5–20	>20% epoch consists of delta (0.5–2 Hz) activity	No eye movement	Chin muscle activity is lower than N1 and N2	Sleep spindles may be present
Stage REM	20–25	EEG is relatively low voltage with mixed frequency resembling N1 sleep	Episodic rapid, jerky, and usually lateral eye movements in clusters	EMG tracing almost always reaches its lowest levels owing to muscle atonia	Phasic and tonic components, the presence of sawtooth waves, alpha waves are 1 to 2 Hz slower than waves occurring during wakefulness and non-REM sleep

EEG, Electroencephalography; EMG, electromyography; EOG, electrooculography; REM, rapid eye movement; SEMs, slow eye movements; TST, total sleep time.

interchangeably in the literature, although subtle differences exist. Additionally, autonomic activation occurs in this state as respiratory and heart rates are increased. Dream recall is also common when subjects are awakened during this stage, whereas dream recall during NREM sleep is relatively rare (Table 23.2).

Sleep stages occur in cycles that repeat approximately every 90 to 120 minutes. A normal sleep cycle begins with N1 and proceeds through N3. Sleep rapidly passes through the same stages in reverse order before REM sleep is initiated, usually first occurring about 90 minutes after sleep onset. Although significant interindividual variation in sleep need is noted, adult humans typically

sleep about 7 to 9 hours per night and spend almost one-third of their life sleeping. Fig. 23.6 provides a graphic representation of the cyclical distribution of sleep states across a single night in a normal healthy adult.

Neurophysiologic Mechanisms

Arousal and Wakefulness

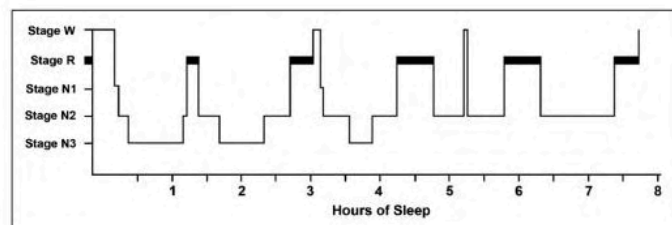
KEY POINT

The neural arousal or activating mechanisms that produce the state of wakefulness reside within multiple brain regions, and each region uses a different neurotransmitter. Activities within brain regions using histamine, norepinephrine, orexin, serotonin, dopamine, and acetylcholine are correlated in the production and maintenance of wakefulness.

In a series of post-mortem examinations of the brains of patients who had died as a result of the outbreak of encephalitis lethargica after World War I, von Economo⁸ observed that lesions in the rostral midbrain and posterior hypothalamus had a profound effect on sleep and wakefulness. He derived two significant correlates from his observations. The first was that lesions in the preoptic and basal forebrain (BF) areas caused severe insomnia. The second was that lesions in the posterior and lateral hypothalamus (LH) caused severe hypersomnia. Based on these data, von Economo hypothesized the existence of a group of sleep-promoting neurons around the hypothalamic optic chiasm and, conversely, a group of wake-promoting neurons in the area of the posterior hypothalamus. Both observations have been proved to be essentially correct, but it was only toward the end of the 20th century that the hypothalamic influences on sleep and wakefulness were integrated into the mechanisms of vigilance state control. Before that, the emphasis had been on brainstem mechanisms and the ascending reticular activating system (ARAS).

Ascending Reticular Activating System

Physiologic analysis of the mechanisms of EEG arousal and wakefulness began with the classic studies of Bremer, who, in 1935, showed that if the brainstem of a cat was completely transected at the level of the midbrain (i.e., to produce the *cerveau isolé*), the result was that the cat maintained a persistent state of sleep. Different interpretations of this result were not possible until Moruzzi and Magoun⁹ demonstrated the existence of an active arousal center below the level of the transaction, in the pons (i.e., the brainstem). Subsequent lesion and electrical stimulation studies identified the brainstem core, or pontine reticular system, as a critical component of arousal and wakefulness. This system was termed the ascending reticular activating system and was morphologically defined by cell bodies that projected from the brainstem to innervate the midbrain and cortex.



• **Fig. 23.6** Sleep hypnogram displaying the distribution of sleep stages across the night.

A more recent advance has been the identification of the importance of a cholinergic activating system in EEG arousal. This is one of the major components of the ARAS, and its identification depends on methods that were developed for labeling neurons that contain specific neurotransmitters. Mircea Steriade (1924–2006) and colleagues¹³ identified cells located near the pons–midbrain junction that increased their discharge rate about 60 seconds before the first change to an aroused state was noted on the EEG. These neurons were found to project to the thalamus, and the change in their discharge rate was the first indication of arousal. Subsequent work identified these neurons as containing the neurotransmitter acetylcholine and being localized to the laterodorsal pontine tegmentum/pedunculopontine tegmentum (LDT/PPT) region.

Cholinergic systems are not the exclusive substrate of EEG arousal. Evidence that multiple systems are involved in arousal and wakefulness comes from the inability of lesions of any single one of these systems to disrupt EEG arousal on a permanent basis.¹⁴ Other brainstem reticular neuronal projections to the thalamus using glutamate neurotransmission and noradrenergic and serotonergic projections from the locus coeruleus and raphe nuclei also play important roles in maintaining wakefulness. In addition to brainstem nuclei, a cholinergic input to the cortex that ascends from the BF nuclei, especially the nucleus basalis of Meynert, plays an important role. Histaminergic neurons localized in the tuberomammillary nucleus (TMN) of the posterior hypothalamus also promote wakefulness. The discovery of the orexin/hypocretin system in 1998 (see the section on Narcolepsy later) led to another CNS arousal system being identified. It is probably the latter hypothalamic systems that were affected in the brains examined by von Economo.⁸

The current conception of the mechanisms of arousal and wakefulness can be summarized by noting that wakefulness and the concomitant EEG arousal is a state of brain activation resulting from the influence of several excitatory neurotransmitters. The term ARAS has been replaced by ascending activating system (AAS). NREM sleep is the absence of such excitatory drive from the onset of sleep through to the deep stages of slow-wave sleep (SWS) (N3). NREM sleep is marked by the gradual reduction of this arousing influence. REM sleep then occurs as a different aroused state, but one that is still modulated by some of the same excitatory pathways that are active during wakefulness. Wakefulness is supported by several, apparently redundant parallel neurotransmitter pathways, which include glutamate, acetylcholine (projecting from both the LDT/PPT nuclei in the brainstem and the BF), and monoamines (i.e., norepinephrine, serotonin, and histamine). With the exception of the hypothalamic TMN and LH projections, which also innervate the cortex, and the cholinergic BF projection, which exclusively innervates the cortex, these ascending projections of the AAS innervate the thalamus.

Thalamic Mechanisms of Arousal

Most AAS projections mediate EEG arousal and wakefulness synapse in the thalamus, which is an essential center for the organization of EEG arousal and maintaining activation at a cortical level. Thalamic mechanisms at a cellular level influence the differences between wakefulness and NREM sleep. A detailed consideration of these thalamic mechanisms is beyond the scope of this chapter; they depend primarily on the cells in the thalamus that project to the cortex (i.e., thalamocortical neurons).¹⁵ Thalamocortical neurons differ in their rate and pattern of discharge depending on the vigilance state. When the arousal-related glutamatergic, cholinergic, noradrenergic, and serotonergic projections are active,

they drive the thalamocortical neurons to discharge in single spike mode. This discharge keeps the EEG in an active state, which contributes to arousal and wakefulness.

In contrast, in the absence of activating or arousing inputs, thalamocortical cells modify their discharge rate to a burst mode. This bursting drives oscillations in thalamic and cortical loop circuits, and these oscillations are the substrate of the slowing and increasing amplitude of the EEG that characterizes NREM sleep. The gradual and continuing reduction in the arousing input results in the gradual deepening of NREM sleep until delta waves dominate the EEG during SWS.

Sleep Onset and Processes That Maintain Sleep

KEY POINT

The neural mechanisms that produce the state of sleep also reside within several brain regions, and each region uses a different neurotransmitter. The onset of activity within the ventrolateral preoptic nuclei orchestrates the onset and maintenance of NREM sleep.

An important consideration is a mechanism that begins this process of reducing the drive from the activating (wakefulness) systems.¹⁶ In other words, how does sleep begin? Electrophysiologic recordings of cells in the BF and anterior hypothalamic regions showed that some of these neurons discharge only during sleep, and this was hypothesized to be an active sleep-promoting mechanism. Confirmation came from studies by Sherin and colleagues,¹⁷ who used anatomic techniques to detect neurons in the ventrolateral preoptic (VLPO) area that was selectively active during NREM sleep. Subsequent immunohistochemical studies identified the neurotransmitters contained in these cells as inhibitory γ -aminobutyric acid (GABA) and galanin. Anatomic work showed neurons containing GABA and glycine projected not only to wakefulness-promoting histaminergic neurons in the TMN and other hypothalamic centers, including the BF, but also to all the brainstem nuclei important in EEG arousal.¹⁸ This group of cells coordinates the inhibition of activity in all components of the AAS to facilitate sleep onset. Current studies continue to investigate the interaction of these neurons with other systems that are important in sleep and, in particular, how other cells within a region around the VLPO area, named the extended VLPO area, are involved with initiating the onset of REM sleep.

Two-Process Model of Sleep Regulation

Homeostatic sleep drive. Sleep propensity is determined by homeostatic and circadian sleep drives. The homeostatic component of sleep need is the sleepiness that follows prolonged wakefulness, and there is now considerable evidence to support the role of adenosine as a mediator of this component. This role of adenosine seems to depend primarily on its inhibitory action on the BF wakefulness-promoting neurons. Commonsense evidence for a sleep-enhancing effect of adenosine comes from the ubiquitous use of coffee and tea to increase alertness because these beverages contain caffeine, an adenosine receptor antagonist.¹⁹ Robert W. McCarley (1937–2017) and colleagues^{20,21} hypothesized that during prolonged wakefulness, adenosine accumulates selectively in the BF and promotes the transition from wakefulness to sleep by inhibiting the wakefulness-promoting BF neurons through its action at the adenosine A1 receptor. Regulation of extracellular adenosine levels depends primarily on metabolic rate: Increased metabolism leads to reduced high-energy phosphate stores and

increased adenosine, which, via an equilibrative nucleoside transporter, leads to increased extracellular adenosine. The BF wakefulness-promoting neurons inhibit the VLPO area, and the adenosine-mediated inhibition of BF cells is one mechanism by which the VLPO cells begin to discharge as sleepiness increases and the sleep episode begins.

KEY POINT

The suprachiasmatic nuclei (SCN) are the neuroanatomic sites of the primary mammalian biologic clock. Subpopulations of SCN neurons exhibit spontaneous patterns of discharge activity and are described as self-sustaining neural oscillators or pacemakers. Cell-autonomous oscillations are observed in SCN neurons dispersed in cell cultures, with periods ranging from 20 to 28 hours.

Circadian process. In addition to the homeostatic need for sleep, sleepiness depends on a second major influence, the circadian phase. Like many other species, humans continue to show regular, circadian sleep/wake cycles and other physiologic and hormonal rhythms in the absence of a 24-hour light/dark (LD) cycle. These rhythms must depend on an internal “clock” or pacemaker that is self-sustaining in the absence of external time cues and can be reset by changes in the environment. The mechanisms of this internal clock have been subject to research over many years, and significant progress has been made using genetic data obtained from a wide variety of species, including the bread mold *Neurospora*, the fruit fly *Drosophila*, and the mouse.²² The diversity of the species from which these results have been obtained emphasizes remarkable conservation of function in time-keeping in biologic systems during evolution.

This circadian influence on sleep also acts through the VLPO area to work in concert with the homeostatic drive to maintain sleep by consolidating the sleep period. The circadian pacemaker achieves this consolidation by a mechanism that, at first sight, seems to be in a paradoxical phase relationship to the normal timing of the sleep period. This assumption follows from the fact that the circadian drive for wakefulness is strongest in the evening hours, just before the normal time of sleep onset. Conversely, the circadian drive for sleepiness is strongest in the morning hours, just before the usual waking time. This process helps consolidate the sleep phase despite the homeostatic drive for sleepiness in the evening and the homeostatic drive for wakefulness in the morning.

Combining the characteristics of the endogenous sleep–wake rhythm with those of a circadian oscillator has led to testable mathematical models of sleep propensity. One of the most significant of these models was developed by Alexander A. Borbély (1939–),^{23,24} who based his model on a two-process single-oscillator model. In this model, sleep is seen as the net result of two processes. One, process S, or sleep propensity, builds during wakefulness and declines exponentially during sleep and is indexed by the delta power of the EEG. As noted earlier, adenosine is a likely candidate for the endogenous mediator of process S. The second process, process C, is an endogenous circadian oscillator that closely parallels core body temperature. The output from the endogenous clock is probably the mediator of process C.

Circadian sleep–wake and physiologic rhythms are treated as sinusoidal variables in this model, assumptions that are not supported by actual data. The sleep/wake state is essentially a binary process, and the actual shape of the variation in physiologic variables across the nycthemeron is asymmetric and is modulated, under normal conditions, by changes related to activity and sleep onset. The recording of core body temperature under several different conditions, including normal expression of the sleep–wake

cycle, sleep deprivation with constant activity over 24 hours, and continuous bed rest with minimal activity but normal sleep–wake behavior, might provide more accurate modeling data after appropriate subtractive manipulation.²⁵ This point is addressed in more detail subsequently.

Circadian Processes and Chronobiology

The circadian processes of sleep and wakefulness are also important for considerations related to pharmacotherapy.²⁶ The basic underlying biologic oscillators affect the response to a drug in addition to driving the biologic rhythms such as sleep propensity and core body temperature.

Circadian Timing System

Biologic rhythms vary systematically across the 24 hours of the nycthemeron. In particular, **circadian rhythms** are driven by endogenous pacemakers that have periods (T, tau) approximating 24 hours.²⁷ As noted previously, these are self-sustained, internally generated biologic signals that, in the natural environment, are normally synchronized or entrained to the 24-hour LD cycle. Both sleep and temporal organization are evolutionarily conserved behaviors, although they can change during the lifespan of an organism.²⁸ Such evolutionarily conserved, the intrinsic temporal order is crucial for human health and well-being, and disturbances in these rhythms result in behavioral, physiologic, psychological, biochemical, and endocrinologic abnormalities.

Studies over many years have attempted to derive an accurate estimation of the period of the endogenous pacemaker. To do so required the subjects not only to be placed under “free-running” conditions in which the environment was completely devoid of any time cues but also under conditions in which the period of the endogenous pacemaker could not be entrained to the rest–activity cycle. These considerations led to the adoption of the forced desynchrony protocol, originally developed by Kleitman in 1938.¹⁰ In this type of study, subjects were kept on a rest–activity cycle that was sufficiently long (e.g., 28 hours) to prevent the entrainment of the endogenous pacemaker to this rhythm. Results were variable, however, until Charles A. Czeisler (1952–) and colleagues²⁹ in 1999 changed the protocol so that their subjects were exposed to very dim light (about 10 to 15 lux) throughout. In this way, Czeisler and colleagues were able to determine the “average period” of the human circadian pacemaker at 24.18 hours; they also reported that healthy older subjects had the same periodicity, with the same stability and precision, as younger subjects.

Under normal circumstances, circadian rhythms become synchronized or entrained to the environmental LD cycle, which acts as a pervasive and prominent synchronizer, or zeitgeber.³⁰ Light signals are received in the retina and are transmitted via a monosynaptic pathway, the retinohypothalamic tract (RHT), to the suprachiasmatic nucleus (SCN). Non–image-forming effects of retinal light exposure range from effects on various physiologic measures, such as shifts in the circadian rhythms of melatonin and body temperature, to effects on psychological measures—for example, high environmental light intensity increases arousal and alertness. Recent evidence demonstrates that the lateral habenula (a key region mediating communication between the forebrain and monoaminergic systems in the midbrain and hindbrain) receives circadian information from the SCN and light signals from the eye that may be able to express intrinsic circadian properties.^{31,32}

Although the mechanism by which light exerts these alerting effects is unknown, a more recently discovered network of blue

light–sensitive retinal ganglion cells (RGCs)^{33,34} is likely part of the input system for the physiologic effects. In animals^{35,36} and humans,³⁷ the suppression of melatonin and shifts in circadian rhythms are particularly sensitive to the short-wavelength, blue component of light. The blue light–sensitive RGCs express the photopigment melanopsin and a neuropeptide, pituitary adenylylate cyclase-activating polypeptide (PACAP).^{33,34,38} Significantly, the RGCs project to brain regions implicated in sleep mechanisms, including the SCN and the VLPO area.^{34,39} This finding suggests that they might mediate the effect of light on sleepiness.⁴⁰

Suprachiasmatic Nucleus: The Central Oscillator

The SCN, which is localized to the anterior hypothalamus, acts as the “biologic clock” to coordinate the circadian rhythm.^{41,42} The SCN receives photic information via the glutamatergic RHT and the geniculohypothalamic tract (GHT), which contains NPY and nonphotic information via serotonergic neurons originating in the dorsal raphe nucleus (DRN). SCN neurons, which project to the dorsomedial and posterior hypothalamic areas and the VLPO area, actively promote and maintain wakefulness during the day and sleep at night (Fig. 23.7). The SCN is involved in the regulation of the timing of sleep–wake states and the expression of the sleep–wake cycle and may play a role in the coordination of specific sleep stages.^{41–43} The role of the SCN in the control of sleep has been studied extensively in several species. In squirrel monkeys, a diurnal species similar to humans, the circadian signal produced by the SCN promotes wakefulness during the subjective day and consolidation of sleep at night. Lesions of the SCN have been found to disrupt the consolidation of both sleep and wakefulness due to a disrupted circadian rhythm.⁴⁴ Neurons in the SCN express two melatonin receptors (MT1 and MT2) with different functional roles.

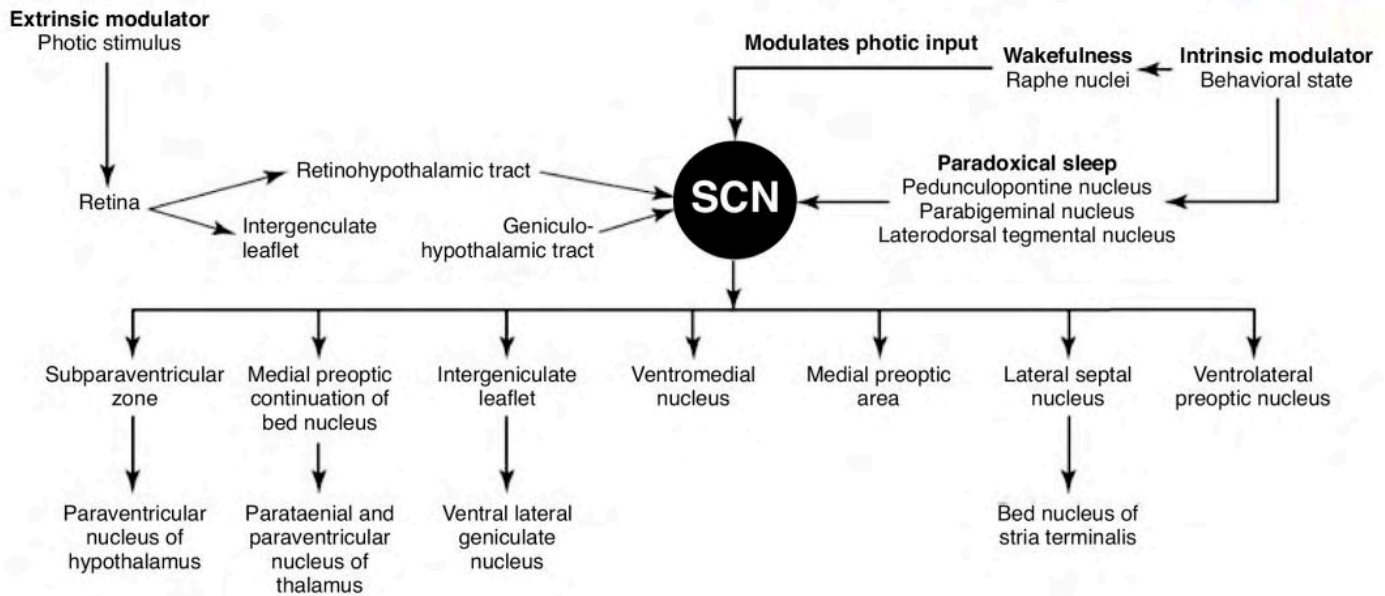
Circadian Rhythm and Metabolism

Sleep and sleep disturbances are viewed increasingly in the context of metabolism. Metabolism and metabolic functions are affected by the time of day and the alignment of the circadian pacemaker to the light/dark cycle.²³ Thus, the anabolic and catabolic processes are segregated in the peripheral tissues, where glycogen and cholesterol synthesis are promoted in the wake-feeding period, and during the sleep-fasting period, gluconeogenesis and glycogenolysis prevail.⁴⁵

Chronopharmacology

Chronobiology is concerned with the mechanisms of periodic biologic influences on health and disease;⁴⁶ pharmacology refers to the medical discipline concerned with the biochemical and physiologic aspects of drug effects, including absorption, distribution, metabolism, elimination, toxicity, and specific mechanisms of drug action. The effectiveness of drugs, also a critical aspect of pharmacology, depends on the pharmacodynamics (i.e., what the drug does to the body) and pharmacokinetics (i.e., what the body does to the drug). These considerations involve the quantitative aspects of drug absorption, distribution, and excretion that are crucial for the design of rational dosage regimens.

Chronopharmacology, or the study of time-dependent variations in pharmacology,⁴⁷ was developed from the inclusion of chronobiologic principles in the study of pharmacology. Traditionally, drug delivery has assumed that a chemical is absorbed predictably from the site of administration. A second-generation drug delivery goal has been the achievement of a continuous constant rate (i.e., zero-order) delivery of drugs. However, living



• **Fig. 23.7** Primary afferent and efferent pathways of suprachiasmatic nuclei (SCN). In addition to the well-described retinohypothalamic tract, which provides SCN with extrinsic stimuli (light), the lesser described serotonergic afferent pathway arising from the raphe nuclei and cholinergic afferent pathways originating in the pedunculopontine, parabigeminal, and laterodorsal tegmentum nuclei are illustrated. This figure graphically illustrates a conceptual model through which intrinsic behavioral state-related stimuli could affect neuronal activity in SCN. (From Decker, M. J., Lee, S. Y., Rye, D. B., et al. [2010]. Paradoxical sleep suppresses immediate-early gene expression in the rodent suprachiasmatic nuclei. *Frontiers in Neurology*, 1, 122.)

organisms are not “zero-order” in their response to drugs. As mentioned earlier, living organisms are predictable resonating dynamic systems governed by intrinsic oscillators, so they require different amounts of drugs at different times within the circadian cycle to maximize the desired and undesired (i.e., chronotoxicity) effects of the drug. Two concepts are important when considering changes in drug efficacy over the 24 hours. The first is circadian changes in drug bioavailability (i.e., chronokinetics), and the second is circadian changes in the susceptibility to the drug (chronesthesia). In brief, clinical chronopharmacology, or chronotherapeutics, is the purposeful alteration of drug levels to match biological rhythms and optimize therapeutic outcomes and minimize side effects.

Melatonin as a Chronobiotic and Chronohypnotic Agent

Drugs that directly influence circadian mechanisms are often referred to as chronobiotics.⁴⁸ The prototype for this type of drug is melatonin (N-acetyl-5-methoxytryptamine), a pineal hormone that has been identified as an important endogenous regulatory factor, with levels that vary with circadian time. Melatonin is an important signal for maintaining endogenous rhythms in synchrony with the environmental LD cycle in humans. Melatonin is exclusively secreted during the subjective night, and its plasma level increases during the evening and declines in the early morning.⁴⁹ The finding that melatonin is secreted primarily during the night and the close relationship between the nocturnal increase in endogenous melatonin and the timing of human sleep have suggested that melatonin might be important in sleep regulation. The onset of melatonin secretion occurs approximately 2 hours before bedtime and has been shown to correlate with the onset of evening sleepiness. In other words, the transition phase from wakefulness and arousal to high sleep propensity coincides with the nocturnal increase in endogenous melatonin. As noted earlier, SCN

neurons express high concentrations of both melatonin receptors, MT1 and MT2, although both receptors are also found widely expressed throughout the CNS. Signaling via MT1 leads primarily to inhibition of activity in SCN neurons.^{50,51} In contrast, the principal MT2-mediated actions in the SCN are related to circadian phase shifts and constitute activation of protein kinase C and increased cell activity.^{52,53}

Melatonin may contribute to sleep initiation by inhibiting the circadian wakefulness-generating mechanisms, an effect that MT1 receptors could mediate in the SCN. Melatonin release is pulsatile during light sleep, and the hormone could function to induce deeper sleep and prevent awakening by continuing to inhibit arousal at the level of the SCN. Overall, the hypnotic and chronobiotic effects of melatonin might be mediated in the SCN and possibly through the MT1 receptor.^{54–56} Induction and maintenance of sleep at the appropriate circadian phase, which could be MT1 mediated, is different from shifting the phase of sleep, which could be MT2 mediated, as a result of an exogenous change in the zeitgeber.

It is relevant that the hypnotic effect of melatonin depends on the circadian phase of administration. Stone and coworkers,⁵⁷ using a double-blind placebo-controlled study, found that melatonin administered at night (23:30 hours) had no significant effect on sleep in healthy individuals, whereas melatonin administered in the evening (18:00 hours) exerted a hypnotic activity. Despite such evidence for the hypnotic action of melatonin, its efficacy in promoting sleep is still controversial, especially because most results show only borderline significance or are otherwise difficult to evaluate because of methodologic inconsistencies.⁵⁸ However, the relatively poor outcomes in these studies in terms of sleep efficiency or total sleep time may be due to the short half-life of melatonin in plasma (less than 30 minutes). A melatonin receptor

agonist having a longer half-life and the ability to occupy SCN receptors for longer periods of time may be more helpful in promoting sleep in insomnia sufferers than melatonin.⁵⁹

Ramelteon is a melatonin receptor agonist that is selective for MT1 and MT2 receptors that has an affinity 3 to 16 times higher than that of melatonin, but without affinity for the melatonin-binding site, quinone reductase 2, previously denoted MT3.^{60,61} Ramelteon has no affinity for other major CNS receptors, including binding sites for neurotransmitters, neuropeptides, regulatory enzymes, or ion channels.^{60,61} However, various additional non-membrane-binding sites of melatonin remain to be tested.⁶²

In 2007, the European Medicines Agency EMA approved a Prolonged Release (PR) form of melatonin 2 mg (Circadin) for the treatment of chronic insomnia typified by poor sleep quality in patients aged >55 years.^{63,64} The PR form peaks in plasma in 2.6 hours after ingestion and is maintained for at least 3.5 hours. Recent evidence suggests that PR melatonin is helpful in the treatment of insomnia comorbid with different neuropsychiatric conditions.⁶⁴

Tasimelteon (HETLIOZ) is an oral agonist of the melatonin both MT1 and MT2 receptors that has been approved in the US Food and Drug Administration (FDA) and EMA to treat non-24-hour sleep-wake disorder⁶⁵ and recently approved by the US FDA to treat nighttime sleep disturbances in Smith–Magenis syndrome (SMS).

Sleep Disorders: Causes and Treatments

As noted at the beginning of this chapter, there are more than 60 identified sleep disorders. Epidemiologic data reveal that the incidence and prevalence of these disorders vary in the general population. Although some of these disorders can be effectively managed by nonpharmacologic therapies or medical management (e.g., CPAP for obstructive sleep apnea), others are treated effectively with pharmacologic agents. Available pharmacologic treatment options for some of these disorders are outlined in this section.

Insomnia

Insomnia is characterized by difficulty in falling asleep (i.e., a sleep latency of greater than 30 minutes), insufficient sleep (i.e., total sleep time of less than 5.5 to 6 hours), multiple nocturnal awakenings, or early morning awakening with inability to resume sleep. Common daytime complaints include somnolence, fatigue, irritability, and difficulty concentrating and performing everyday tasks. In addition, subjects with a diagnosis of insomnia are at higher risk for illness and for injury caused by drowsiness while driving. Because insomnia is associated with difficulty in concentration, it is a major risk factor for accidents.⁶⁶ Insomnia is a common complaint that affects 30% to 35% of the US adult population and is chronic in about 10%.⁶⁷ The risk of insomnia is greatest in elderly adults. The adverse physiologic and psychological sequelae of insomnia have a major negative impact on the quality of life in affected individuals.^{68,69} Almost 10% of people with chronic insomnia have daytime consequences of fatigue, irritability, and impaired concentration that affect health, mood, and normal functioning. With reduced productivity and an increased risk of accidents, the overall economic burden of insomnia is estimated to be 1% of the gross domestic product.^{70–72} Insomnia is also experienced as a stressor by patients who have major depressive disorders, and disturbed sleep has been identified as a hallmark of depression; this is not consistently recognized in clinical practice.

Pharmacologic treatment of insomnia in the last few decades has been based on several classes of medication (Table 23.3).

Benzodiazepines were introduced in the 1970s and rapidly increased in popularity because of their efficacy and relative safety compared with barbiturates, carbamates, chloral derivatives, and methaqualone. In recent years, however, prescriptions for benzodiazepines have declined because of their associated side-effect profile, including the tendency of benzodiazepines to promote dependence, the occurrence of rebound insomnia after withdrawal of short-acting and intermediate-acting derivatives, and the loss of efficacy after a few weeks of treatment. The reduction in benzodiazepine use has also coincided with the introduction of a structurally dissimilar group of nonbenzodiazepine derivatives, including the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem, and the pyrazolopyrimidine compound zaleplon.

A new class for the management of insomnia is dual orexin receptor (OXR) antagonists that block OXR1 and OXR2 and enhance sleep through a decrease in arousal signaling.⁷³ Currently, two drugs of this class have been approved by the US FDA, suvorexant (Belsomra) in 2014 and lemborexant (Dayvigo) in 2019. This class of drugs has been observed to curtail REM latency and increase total sleep time, primarily through increasing REM sleep.⁷³ This class of drugs does not appear to be associated with tolerance, withdrawal, or rebound insomnia if suddenly withdrawn.⁷³

Restless Legs Syndrome and Periodic Limb Movement Disorder

The first clinical description of RLS was made in the 17th century by Willis, an English physician, who stated, “Wherefore to some, when being abed they betake themselves to sleep, presently in the Arms and Legs, leaping and Contractions of the tendons, and so great a Restlessness and Tossing of their members ensue, that the diseased are no more able to sleep than if they were in a Place of greatest torture.” More than 200 years later, the physician Ekbom coined the phrase “restless legs” and stated that “the syndrome is so common and causes such suffering that it should be known to every physician.”

RLS is now recognized as a chronic and progressive neurologic disorder characterized by unpleasant sensations in the legs and a compelling urge to move them while the patient is awake. These symptoms occur most frequently during the evening or at night as well as during periods of rest. Approximately 5% to 15% of European and US populations are affected by RLS. Adverse outcomes associated with RLS include hypertension, alcohol abuse, neurocognitive deficits, and decrements in mental and physical health. Patients with RLS report an urge to move their limbs during the daytime if they become confined in a delineated space for extended periods, for example, having to sit at a desk. Unpleasant sensations in the limbs typically combined with urges to move the legs occurring in the evening often lead to difficulties with sleep onset or sleep maintenance. When these symptoms are experienced by children, they have often been incorrectly identified as “growing pains.”

Periodic limb movements during sleep (PLMS) are frequently associated with RLS. PLMS is defined as periodic episodes of spontaneous, repetitive, and highly stereotyped involuntary limb movements that occur during sleep. Four or more repetitive muscle contractions lasting 0.5 to 5 seconds and separated by 4 to 90 seconds are conventionally regarded as indicative of PLMS. The night-to-night variability in their occurrence and variability in the intensity of daytime and evening sensory symptoms often lead to PLMD being underappreciated or missed during a clinical evaluation. Chronic sleep restriction and sleep fragmentation is one adverse outcome

TABLE 23.3 Medications Approved by US Food and Drug Administration for Treatment of Insomnia

Medication	Trade Name	Dose (mg)	Half-Life (hr)	DEA Schedule
BZD Receptor Agonists				
Immediate-Release BZDs				
Estazolam	ProSom	1, 2	10–24	IV
Flurazepam	Dalmane	15, 30	2.3 (active metabolite: 48–160)	IV
Quazepam	Doral	7.5, 15	39 (active metabolite 73)	IV
Temazepam	Restoril	7.5, 15, 22.5, 30	3.5–18.4	IV
Triazolam	Halcion	0.125, 0.25	1.5–5.5	IV
Immediate-Release Non-BZDs				
Eszopiclone	Lunesta	1, 2, 3	~6 (~9 in elderly)	IV
Zaleplon	Sonata	5, 10	1	IV
Zolpidem	Ambien	5, 10	~2.5	IV
Modified-Release Non-BZDs				
Zolpidem CR	Ambien CR	6.25–12.5	2.8 in males (longer in females)	IV
Nonbenzodiazepines Alternate Delivery				
Zolpidem oral spray	Zolpimist	5, 10	2.7–3.0	IV
Zolpidem sublingual	Edluar	5, 10	~2.5	IV
Zolpidem sublingual	Intermezzo	1.75, 3.5	~2.5	IV
Selective Melatonin Receptor Agonist				
Ramelteon	Rozerem	8	1–2.6	None
Histamine Receptor Antagonist				
Doxepin	Silenor	3–6	15	None
Orexin receptor antagonist				
Suvorexant	Belsomra	5, 10, 15, 20 mg	12	IV
Lemborexant	Dayvigo	5, 10 mg	17–19	IV

BZD, Benzodiazepine; DEA, Drug Enforcement Administration.

attributed to both RLS and PLMD; this is believed to contribute to the deleterious physical, mental, and social effects associated with the disorders. Consequently, the negative impact of RLS on quality of life is similar to that observed with other chronic disorders such as depression, heart failure, and diabetes.

More recent epidemiologic and genetic linkage studies distinguish two forms of RLS: early-onset, or primary, RLS, and late-onset, or secondary, RLS. The early-onset form typically begins in childhood or young adulthood with a gradual progression in symptom severity. Early-onset RLS is inherited in an autosomal dominant fashion, shows genetic anticipation, is twice as prevalent in females, and is associated with at least two separate genetic loci.⁷⁴ In addition, PLMD is more typically associated with this form of RLS.

Late-onset RLS is characterized by a later age of symptom onset, usually older than 45 years; an equal female-to-male ratio; a rapidly progressive course; and a relationship with anemia and other associated identifiable causes such as diabetes, kidney disease, neuropathy, and even nervous system trauma.⁷⁴ In addition to these intrinsic pathophysiologic mechanisms, certain extrinsic factors are associated with increased frequency and severity of

symptoms. H₂ histamine antagonists such as ranitidine or cimetidine have been reported to worsen symptoms of RLS.⁷⁵ Caffeine, alcohol, and some antidepressants, including fluoxetine, also are reported to worsen the frequency and severity of RLS or PLMD symptoms.⁷⁶ Epidemiologic studies suggest that the onset of RLS increases with age, with a prevalence rate of 2% in children, 3% in 30-year-olds, and up to 20% in 80-year-olds. Genetic studies and linkage analyses also show that early-onset RLS is a heritable trait, but the pathophysiologic mechanisms of RLS remain unclear.⁷⁴

Because of the essential motor component of the disorder, dopamine deficiencies may contribute to the etiology of RLS and PLMD. Research has focused on determining if reductions in extracellular dopamine levels within the CNS or deficiencies in postsynaptic responsivity to dopamine might contribute to the symptoms of RLS and PLMD. Reduced extracellular dopamine levels are central to several hypotheses regarding neurochemical substrates contributing to RLS. However, elucidation of any actual dopaminergic dysfunction has remained enigmatic. It's possible that decreased extracellular dopamine is caused by decreased dopamine production or greater sequestration inside cell bodies

and terminals. Alternatively, dopamine production and release may be normal, but the number or type, or both, of postsynaptic dopamine receptors, may be altered and so result in the symptoms.

The first link made between dopamine and RLS was based on the observation that many patients derived relief from dopamine augmenting drugs. This was acknowledged in the “Practice Parameters for the treatment of RLS and PLM,”⁷⁷ which stated that dopaminergic agents are the best-studied and most successful agents for the treatment of RLS and PLMD. Following multiple clinical trials with dopamine-enhancing compounds, levodopa with decarboxylase inhibitors and dopamine agonists such as ropinirole and pramipexole were found to be the most effective for the treatment of RLS and PLMD.⁷⁷ Despite the promise that dopamine-enhancing compounds can reduce RLS symptoms, it should be noted that their use for RLS is currently approved only for adults; data are lacking with regard to their use for RLS in pediatric populations and during pregnancy. When prescribing any type of dopaminergic medication for RLS symptom relief, the potential for side effects, such as nausea, gastrointestinal distress, reduced blood pressure, and sleepiness, should be taken into account and discussed with a sleep medicine physician. In addition, because dopamine modulates mood, cognition, wakefulness, and sleep, any dopamine precursor, agonist, or antagonist can feasibly result in acute thought and behavioral changes. Given that most RLS patients need very low doses of dopaminergic medications for symptomatic relief, the likelihood of a serious or adverse outcome is remote. Recently, calcium channel $\alpha_2\delta$ ligands have been shown to be effective in treating RLS symptoms with no reported augmentation.⁷⁸ Gabapentin enacarbil⁷⁹ is the only drug in this class officially approved for RLS (Table 23.4).

There is good evidence indicating that RLS patients have lower than normal iron stores in certain brain regions even if the patient has no anemia; therefore, iron therapy can be beneficial in selected patients.⁸⁰ A consensus of RLS experts recommended that all RLS patients with serum ferritin concentration of 75 mg/L or less and transferrin saturation of less than 45% have to receive a trial of oral iron therapy.⁸⁰ Nevertheless, it should be remembered that systemic measures of iron status do not always predict those who will respond to iron treatment. In patients with moderate to severe

chronic persistent or refractory RLS and serum ferritin concentration is between 76 mg/L and 100 mg/L, intravenous administration of iron should be considered.⁸¹ Also, intravenous iron therapy should be considered if oral iron is not adequately absorbed because of malabsorption disorders, oral iron is not tolerated, or RLS symptoms do not improve despite a 3-month trial of oral iron.⁸¹ All of the intravenous iron preparations approved by the FDA to treat iron deficiency anemia can be used to treat RLS.⁸¹

Narcolepsy

The earliest clinical descriptions of narcolepsy were documented by the German physician Westphal in 1877 and by Fisher in 1878. However, the French physician Gelineau, writing in 1880, is generally acknowledged as the first clinician to recognize narcolepsy as a distinct clinical entity. Initial descriptions included characterization of excessive daytime sleepiness and “sleep attacks.” Although all three of these early descriptions documented the appearance of sleep attacks, they did not discern the symptoms of sudden muscle weakness triggered by an emotional event (i.e., cataplexy) as separate from the sleep attack event. This is most evident from the first description of narcolepsy as a clinical entity: “I propose to give the name of narcolepsy (“*narco* $\equiv$ somnolence” and “*lepsy* $\equiv$ seized by”) to a rare neurosis or at least little known until now, characterized by a mandatory need to sleep, sudden and of short duration, that recurs at more or less close intervals.”⁸² In 1902, Loewenfeld recognized that emotion-induced muscle weakness was a separate feature of the disorder and first used the term cataplexy to describe it.⁸³

Today, narcolepsy is characterized by a tetrad of clinical symptoms. Two features of the tetrad—persistent excessive daytime sleepiness and cataplexy—were documented in the original descriptions of the disorder and remained the only two clinical features essential for diagnosis. The recognition of two additional features—hypnagogic hallucinations (the onset of dreams while still awake) and sleep paralysis (a temporary loss of muscle tone or an inability to perform voluntary movements either at sleep onset or on awakening)—were added later.⁸⁴ Another common symptom of narcolepsy is fragmented sleep with multiple arousals and awakenings at night.

TABLE 23.4 Pharmacologic Management of Restless Legs Syndrome

Drug	Dose (mg/day)	Time To Peak Plasma Level (min)	Half-Life (hr)	Mode of Elimination
Levodopa	100–400	30	1.5–3	Hepatic
Carbidopa/Levodopa	10/100–25/250	120	6–8	Hepatic
Bromocriptine	2.5–10	45–60	3–4 (up to 40)	Hepatic
Cabergoline	0.25–3.0	120	63–68	Hepatic
Pramipexole	0.25–1.5	120	8–12	Renal
Ropinirole	0.5–4.0	60–120	Approximately 6	Hepatic
Rotigotine patch	1–3 mg/24 hours	Approximately 24 hr post-application	5–7	Renal
Gabapentin enacarbil	300–1200 mg day	180	5–6	
Methadone	2.5 mg and 20 mg/day	150 to 240	12–18 hours with a mean of 15 hours	Hepatic

Narcolepsy may not be as rare a disorder as once thought; according to the National Institute of Neurological Disorders and Stroke (NINDS), narcolepsy is an underrecognized and underdiagnosed condition. Nevertheless, in the United States, narcolepsy is the third most frequently diagnosed primary sleep disorder after sleep apnea and RLS. Current estimates suggest that 1 in about 2000 Americans are narcoleptic. The prevalence of narcolepsy is significantly greater in Japan, affecting 1 in 600 people, but substantially less in Israel, affecting only 1 in 500,000, although differences in diagnosis may account for at least part of this variation. There is no gender difference in the prevalence of the disorder.

The onset of narcoleptic symptoms typically occurs between the ages of 15 and 30, although there are reports of symptom onset occurring in very young children and adults older than 30. In addition, it is not unusual for 12 years to elapse between the initial onset of symptoms and a definitive diagnosis. Up to 10% of patients diagnosed with narcolepsy report that a close relative has similar symptoms. The familial association of narcolepsy was recognized in the early descriptions, as noted in the mother of the narcoleptic patient first examined by Westphal and the sister of the first narcoleptic patient described by Fisher. Such familial clustering suggests a genetic origin for this disorder. Although immediate family members of narcoleptics are at a statistically greater risk of developing the disorder, this risk is low compared with purely genetic disorders and indicates that other factors must be involved.

Most cases of narcolepsy are sporadic and occur without evidence of genetic inheritance. Until more recently, the etiology of narcolepsy was unknown, but it was associated with the specific human leukocyte antigen (HLA) allele, DQB10602, and often in combination with HLA-DR2 (DRB115). In 1998, two research groups first described, clustered around the lateral and perifornical hypothalamus, a group of cells that contained a previously unknown neurotransmitter.^{85,86} These cells contained orexin/hypocretin, and based on the neuroanatomy, they were hypothesized to be involved in the regulation of sleep and wakefulness. However, physiology suggested a major role in food intake and energy balance, which was the focus of research during the first 12 months. Within 1 year of the discovery, however, two independent groups discovered in 1999 that the clinical symptoms of narcolepsy were associated with a loss or dysfunction of orexin/hypocretin-containing cells.^{87,88}

Following the initial descriptions of narcolepsy, various empiric treatments were tried with little success. Among these were spinal fluid taps, intrathecal air injection, x-ray irradiation of portions of the hypothalamus, and later ephedrine administration. In 1935, Prinzmetal and Bloomberg synthesized a new compound, benzedrine, the original drug in the class later known as amphetamines. Although originally developed to treat nasal congestion, it had no effect on the nasal mucosa, but when given orally, benzedrine led to a reduction in weight, and it was soon routinely used as an appetite suppressant. Subsequently, the CNS-stimulating effect of the amphetamines was recognized, leading to their use to treat hypersomnolence. For many years, a regimen of amphetamines in conjunction with a tricyclic antidepressant such as imipramine, which reduces REM sleep, was the standard pharmaceutical intervention for narcolepsy. Then, modafinil, armodafinil, solriamfetol, pitolisant, and nonamphetamine wake-promoting agents, were developed.

With a side-effect profile free from addiction, tolerance, and other adverse outcomes associated with amphetamines, modafinil/armodafinil soon became the treatment of choice for alleviating

the symptoms of excessive daytime sleepiness associated with narcolepsy. Solriamfetol is a selective dopamine and norepinephrine reuptake that the US FDA recently approved in 2019 to treat excessive sleepiness in narcolepsy and obstructive sleep apnea patients.^{89,90} It is well tolerated and an alternative to modafinil or armodafinil. Moreover, it does not cause cardiac side effects, rebound hypersomnia, or withdrawal effects.⁸⁹ Recently, published data on the treatment of narcolepsy with pitolisant, a small molecule acting as an antagonist/inverse agonist at the presynaptic H3 receptor subtype that enhances the activity of histaminergic neurons, are promising.⁹¹ Currently, the drug is approved by the European Union (EU) and the US FDA to treat EDS in narcolepsy in adult patients with and without cataplexy. The US FDA has also approved it for the treatment of cataplexy.⁹² A network meta-analysis of 14 randomized clinical trials (RCTs) demonstrated that pitolisant, modafinil, and sodium oxybate have similar efficacy in reducing EDS; however, only sodium oxybate and pitolisant were observed to have comparable efficacy on cataplexy.⁹³ Another recent noninferiority meta-analysis of RCTs demonstrated that pitolisant was noninferior to modafinil in alleviating EDS; however, it was superior to modafinil in reducing cataplexy.⁹⁴ A concern of pitolisant is that it can disturb nocturnal sleep due to its wake-promoting properties.⁹¹

In 2002, sodium oxybate (Xyrem), known as gamma-hydroxybutyric acid (GHB), a CNS depressant, gained US FDA approval for the treatment of excessive daytime sleepiness and cataplexy in narcoleptic patients.⁹⁵ The use of a CNS depressant may seem counterintuitive as a strategy for treating excessive daytime sleepiness. However, sodium oxybate, taken immediately before sleep and again 2 to 4 hours later, causes an increase in SWS, reduces the number of nocturnal awakenings, and enhances sleep continuity.⁹⁶ The result is a reduction in daytime sleepiness and cataplexy and a less fragmented sleep period. The mechanism by which sodium oxybate reduces excessive daytime sleepiness and cataplexy is unknown, but it may involve the activation of GABAB receptors.⁹⁵

Two recent forms of sodium oxybate have been released. Calcium, magnesium, potassium, and sodium oxybate (Xywav) is a lower sodium alternative to sodium oxybate that has been approved in the United States for treating cataplexy and EDS in narcolepsy patients. It contains the same active portion as sodium oxybate with 92% less sodium, which may provide a safer alternative for narcolepsy patients with heart failure, hypertension, or renal impairment.⁹⁷ Another formulation is FT218, an extended-release sodium oxybate for once-nightly administration is under review at the US FDA for treating EDS and cataplexy in adults patients with narcolepsy.⁹⁷ In addition, the sodium oxybate indications have recently been extended to include treatment of children (≥ 7 years of age) with narcolepsy,⁹⁸ based on a recent placebo-controlled, double-blind, randomized clinical trial that established its efficacy, safety, and tolerability in children and adolescents with narcolepsy.^{99,100} The American Academy of Sleep Medicine (AASM) has put a conditional recommendation to use sodium oxybate for the treatment of narcolepsy in pediatric patients.¹⁰¹ A few other potential therapies for EDS in narcolepsy are under development.⁹⁸

Determining the most appropriate treatment for a narcoleptic patient is influenced by several factors, including age, the severity of symptoms, presence or absence of cataplexy, other medical conditions, and concomitant medications. Conservative treatment of narcolepsy involves administering two or more medications with a stimulant for excessive daytime sleepiness, a tricyclic antidepressant, serotonin selective reuptake inhibitors (SSRIs), or

serotonin-norepinephrine reuptake inhibitors (SNRIs) for cataplexy, and a hypnotic for insomnia and fragmented nocturnal sleep. A young narcoleptic patient without cataplexy may achieve some relief of symptoms by maintaining a fixed schedule of sleep time combined with prescheduled daytime naps (strategic naps), if feasible. This approach ensures an adequate opportunity for sleep and coupled with an alerting compound such as modafinil or armodafinil (the R-enantiomer of modafinil with a longer half-life of 10 to 15 hours), it may help to restore a functional level of daytime alertness.

In contrast, a patient presenting with more severe symptoms, including cataplexy, hypnagogic hallucinations, and sleep fragmentation, may require aggressive treatment. In addition to good sleep hygiene, an amphetamine such as methylphenidate might be prescribed to help sustain daytime wakefulness, together with sodium oxybate. This regimen could be combined with an SSRI, an SNRI, or a tricyclic antidepressant to treat cataplexy and the other symptoms of REM sleep dysregulation, including hypnagogic hallucinations. In a patient with sleep fragmentation, sodium oxybate is often useful because sleep continuity is enhanced, and excessive daytime sleepiness and cataplexy are controlled. Cataplexy and hypnagogic hallucinations require additional agents such as sodium oxybate, an SSRI, or a tricyclic antidepressant. Nonpharmacologic therapies, such as scheduled naps, regular sleep and wake schedules, and proper sleep hygiene, are essential elements of any successful treatment regimen.

The AASM has recently published a clinical practice guideline for the treatment of central disorders of hypersomnolence based on the currently available evidence.¹⁰¹

Recent developments include the 2021 US FDA approval of calcium, magnesium, potassium, and sodium oxybates (Xywav) as the first indicated treatment for idiopathic hypersomnia in adults. A phase 3 double-blind, placebo-controlled, randomized trial demonstrated statistically and clinically significant improvements in the Epworth Sleepiness Scale score, Patient Global Impression of Change, and the Idiopathic Hypersomnia Severity Scale.¹⁰²

Parasomnias

Parasomnias are undesirable motor, sensory, or behavioral phenomena that occur primarily during sleep.¹⁰³ These phenomena range from normal to abnormal and from benign to potentially lethal and can be associated with normal developmental processes or neurodegeneration. The ICSID-3 lists several parasomnias encompassing NREM sleep (arousal disorders), REM sleep-related disorders, and other parasomnias such as exploding head syndrome, sleep-related hallucinations, sleep enuresis, and parasomnia due to a medical disorder or a medication.² The focus here is on more common NREM and REM sleep parasomnias. NREM sleep parasomnias, also termed arousal disorders, include confusional arousals, sleep terrors, sleepwalking, and sleep-related eating disorder. The pathophysiologic mechanisms underlying arousal disorders are still unknown, but current hypotheses suggest that they may result from the brain being simultaneously in a state of partial wakefulness and NREM sleep. This state leads to an ability to perform complex motor or verbal actions without conscious awareness of the actions.

Primary arousal disorders share several common factors, including familial clustering, which suggests a genetic predisposition, childhood predominance, and a tendency to occur during NREM sleep. Confusional arousals are characterized by episodes of marked mental confusion during or after an arousal from sleep.

They usually occur during the first third of the night, last 30 seconds to 5 minutes, and may be accompanied by mumbling or automatic behaviors, or both. During the event, the person does not leave the bed, and there are no signs of fear or terror. Following confusional arousal, the individual usually falls back to sleep with no recollection of the event (i.e., retrograde amnesia) on awakening. Triggers for confusional arousals include anything that either fragments sleep or enhances SWS. Examples include environmental factors such as noise or temperature, stress, fever, pain, pregnancy, recovery from sleep deprivation, or CNS-active medications. As noted earlier, youth, a family history, and a history of being a deep sleeper are predisposing factors.

Sleep terrors, which are observed primarily in children, are similar to confusional arousals and occur during the first third of the night. They also begin in NREM sleep, typically during SWS at a time when an episode of REM sleep would be expected, and last 30 seconds to 5 minutes. The triggers for sleep terrors are similar to those for confusional arousals; the principal difference is that sleep terrors are accompanied by an abrupt awakening, intense vocalization, and inconsolable fear or terror. Sleep terrors most frequently occur in children 5 to 7 years old and appear with equal prevalence in boys and girls. Most children with sleep terrors outgrow them by 8 years of age, although about 30% may continue to experience them into adolescence; only about 1% experience sleep terrors as adults.

Another parasomnia, somnambulism or sleepwalking, also occurs during NREM sleep but is characterized by the presence of automatic behaviors of varying complexity, including walking, eating, mumbling, and, rarely, violence. The duration of these episodes can be 15 minutes to several hours. The episode is usually self-limiting and terminates with a return to sleep. Clinical evidence shows that attempts to intervene may be met with resistance and outbursts.

As with other NREM sleep parasomnias, the familial clustering of somnambulism suggests a genetic predisposition. Triggers for somnambulism, such as sleep fragmentation and increased depth or duration of SWS, are similar to those of the other arousal disorders. The age of onset for somnambulism is about 5 years, with the highest prevalence at about 12 years of age. Somnambulism can occur in 15% to 30% of children and young adolescents, equally affecting boys and girls. Most children who are sleepwalkers typically outgrow the events by age 15, but 1% may continue to experience episodes in adulthood.

The sleep-related eating disorder is usually associated with sleepwalking and involves partial arousals from sleep and engagement in involuntary eating or drinking. As with other arousal parasomnias, patients have limited or no recall of the events. Foods consumed can consist of unusual combinations or even inedible/toxic substances such as coffee grounds, cake mixes, frozen or uncooked products, eggshells, or cleaning materials. Patients may have unexplained weight gain and morning anorexia. Certain medications have also been reported to induce sleep-related eating disorder (e.g., zolpidem, anticholinergics, and lithium).¹⁰³

Another clinically identifiable category of parasomnias occurs during REM sleep and, for this reason, typically in the second half of the night. These include REM sleep behavior disorder (RBD), nightmare disorder, and isolated sleep paralysis. In contrast to NREM arousal disorders, REM sleep parasomnias usually affect adults more frequently than children, and they do not exhibit a genetic pattern of inheritance. RBD, in particular, is associated with neurodegenerative disorders such as Parkinson's disease and multiple system atrophy and usually occurs in older men. It has

also been reported in patients with narcolepsy and in association with alcohol and some medications such as antidepressants and β -blockers.¹⁰⁴ Symptoms may rarely include violent dream enactment behavior owing to a loss of atonia during REM sleep. However, in most cases, there could be minimal movements during REM sleep. If left untreated, RBD can cause serious injury to the patient and the sleeping partner. During the attack, polysomnography shows loss of normal electromyographic atonia, which is called REM sleep without atonia (RWA).

Treatment for NREM and REM sleep parasomnias frequently includes avoidance of potential triggers and, in the case of somnambulism and RBD, necessitates a safe, well-monitored sleeping environment. There are no randomized controlled trials of treatments for NREM and REM parasomnias. The most common pharmaceutical treatment for REM and NREM sleep parasomnias is usually a longer-acting benzodiazepine. Through the reduction of both SWS and REM sleep time and the number of transitions between sleep states, benzodiazepines essentially reduce the occurrence of the state in which an arousal disorder or RBD episode can occur. Benzodiazepines were initially developed as anxiolytics and subsequently as hypnotics. The success of the first compounds led to further research and development, and many compounds of this class eventually became available. Notable hypnotic benzodiazepine compounds are nitrazepam (Mogadon), temazepam (Restoril), flurazepam (Dalmane), and midazolam (Versed); others, such as clonazepam (Klonopin), are frequently used in the treatment of parasomnias and as antiseizure medications.

Considerations for employing benzodiazepine compounds in treatment include their half-life (i.e., the time required for one-half of the active drug to be metabolized or eliminated from the body). Short-acting benzodiazepines have half-lives of 6 to 8 hours or less, but long-acting benzodiazepines have half-lives that often exceed 24 hours. A gradual increase in the blood levels of a longer-acting drug has the potential to cause residual effects. A benzodiazepine taken in the evening to reduce the likelihood of experiencing an arousal event may induce residual sleepiness the next day. Regarding their use for the treatment of arousal disorders, apart from their role in reducing the overall duration of time in states, as noted earlier, no definitive conclusions are yet possible concerning their mechanism of action. Clonazepam, as a longer-acting benzodiazepine, is a frequent first choice, although the careful selection of the appropriate benzodiazepine for a particular patient is essential to reduce the likelihood of residual daytime sleepiness. This is especially important to consider when treating parasomnias because many patients are children or elderly adults.

For REM parasomnias, small case series and case reports describe the efficacy of a wide range of medications, most prominently clonazepam but also melatonin, pramipexole, acetylcholinesterase inhibitors, paroxetine, L-DOPA, zopiclone, temazepam, triazolam, alprazolam, Yi-Gan San, desipramine, carbamazepine, clozapine, and sodium oxybate.¹⁰⁴

SELF-ASSESSMENT QUESTIONS

1. What is the *International Classification of Sleep Disorders, 3rd Edition*, and what information does it contain?
2. What are the electroencephalographic correlates of wakefulness and sleep stages N1, N2, N3, and REM?
3. What type of drug had been used for centuries to promote sleep onset and maintenance?
4. What class or classes of drugs have replaced opium?

5. How many people in the United States experience chronic sleep disorders?
6. Who was von Economo, and what theories guided his neuroanatomic exploration of brain regions involved in the processes of initiating and maintaining wakefulness and sleep?
7. What is the ascending activating system (AAS)?
8. How do neurons within the ventrolateral preoptic (VLPO) area affect sleep?
9. What are the suprachiasmatic nuclei (SCN), and what are intrinsic discharge properties exhibited by many of its neurons?
10. Define chronobiology and chronopharmacology.
11. Describe pharmacologic treatments for insomnia.
12. What is the difference between restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)?
13. What is the tetrad of clinical symptoms that defines narcolepsy?
14. Give two examples of a parasomnia, and name the class of drugs routinely used in the treatment of these sleep disorders.
15. What types of principal complaints characterize insomnia, and what drug classes are used to treat this disorder?

CLINICAL SCENARIO

A 59-year-old White man with a body mass index of 27 and a history of hypertension, arthritis, and depression presents to the sleep clinic with chief complaints of excessive daytime sleepiness, awakening from nocturnal sleep after 2 to 3 hours, and prickly sensations in the legs that coincide with nocturnal awakenings but are temporarily relieved by walking. He also reports experiencing the same prickly sensations in his legs during long trips in the car, regardless of the time of day. The sensations in his legs also occur spontaneously two to three times a week, during the evening hours.

The patient underwent full overnight **polysomnography** during which the following parameters were monitored: electroencephalography (EEG), electrooculography (EOG), submental and leg electromyography (EMG), electrocardiography (ECG), oxyhemoglobin saturation, respiratory effort, and nasal and oral airflow. Analysis of data revealed a sleep efficiency of 94% with a sleep latency of 5 minutes. The arousal index was 15 arousals per hour of sleep. The distribution of sleep stages was notable for an increased amount of N2 and REM sleep with a reduced amount of N3 sleep. The REM latency was normal.

Periodic leg movements occurred 41 times per hour of sleep and resulted in 11 arousals per hour of sleep. No arrhythmias were noted on ECG. No snoring was noted with the patient in the lateral position. The apnea/hypopnea index (number of apneas and hypopneas per hour of sleep) was mildly elevated at 8.2, with a further increase to 13.6 events per hour during REM sleep. Oxyhemoglobin desaturation reached a nadir of 82% in REM sleep and 86% in non-REM sleep.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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Appendix A

Answers to Self-Assessment Questions and Clinical Scenarios

Chapter 1

Self-Assessment Questions

1. What is the definition of the term *drug*?
Answer: A drug may be defined as any chemical that alters an organism's function.
2. What is the difference between the generic name and trade name of a drug?
Answer: The generic name of a drug is nonproprietary, whereas the brand name is the name given by a particular manufacturer of the drug. If a physician prescribes a particular brand of a drug, the pharmacist must sell that brand unless generic substitution is indicated on the prescription.
3. What part of a prescription contains the name and amount of the drug being prescribed?
Answer: The inscription.
4. A physician's order reads as follows: "gtt IV of racemic epinephrine, ccc of normal saline, q4h, while awake." What has been ordered?
Answer: Four drops of racemic epinephrine with 3 cc of normal saline, to be given intravenously every 4 hours while the patient is awake.
5. The drug salmeterol was released for general clinical use in the United States in 1994. Where would you look to find information about this drug, such as the available dosage forms, dosages, properties, side effects, and action?
Answer: Several sources of information would be available on a new drug in addition to research reports in the journal literature: the package insert with the drug, the *Physician's Desk Reference* (PDR), and the United States Pharmacopeia–National Formulary (USP–NF). Usually a new drug release is accompanied by the manufacturer's marketing literature, which is available from drug representatives or at conferences.

Clinical Scenario

Subjective: He played golf on a newly mown course. He had exhibited allergies in the past few years and was diagnosed as having asthma. He began to experience difficulty breathing later in the day, with wheezing and some shortness of breath on mild exertion. His heart rate increased from 66 to 84 beats/min, and he felt shaky. By midnight, his wheezing had returned. He continued using Primatene Mist through the next morning. A friend found him later that evening audibly wheezing, gasping for air, and in severe respiratory distress.

Objective: No objective data were presented in the scenario. Although some information may be misconstrued as objective, it is not. All objective data must be obtained by a health care professional during the physical examination.

Assessment: Failure to seek medical help while self-treating with an over-the-counter (OTC) drug product. He probably did not realize that (1) Primatene Mist is epinephrine, which is short acting (1–2 hours in duration) and will not control the full development of an asthma exacerbation, termed the *late-phase* reaction; and (2) a progressive asthma episode can cause serious obstruction of the airway and often worsens in the evening or night. Given his continued symptoms, he required more aggressive therapy than Primatene Mist.

Plan: Intubate and ventilate the patient. Place the patient on inhaled albuterol or levalbuterol. Inhaled anticholinergic may be of benefit. Start the patient on intravenous (IV) steroids.

Chapter 2

Self-Assessment Questions

1. If a drug is in liquid solution, what routes of administration are available for its delivery, considering only its dosage form?
Answer: Oral, injection, inhalation (nebulization), and topical (possibly). The type of drug, pharmacokinetics, and intended effect will further narrow the choice of route of administration.
2. Although generic drug equivalents all have the same amount of active drug, do formulations of the same drug from different manufacturers all have the same ingredients?
Answer: No, not necessarily. Ingredients other than the active drug may differ. For example, in a tablet preparation, the substances used to form the active drug into a molded tablet may vary.
3. If 200 mg of a drug results in a plasma concentration of 10 mg/L, what is the calculated volume of distribution (V_D)?
Answer: $V_D \equiv 200 \text{ mg} / (10 \text{ mg/L}) \equiv 20 \text{ L}$.
4. If the V_D of a drug, such as phenobarbital, is 38 L/70 kg, and an effective concentration is 10 mg/L, what loading dose would be needed for an average adult (assuming total bioavailability)?
Answer: $\text{Dose} \equiv V_D \times \text{concentration} \equiv 38 \text{ L} \times 10 \text{ mg/L} \equiv 380 \text{ mg}$.
5. If an inhaled aerosol has zero gastrointestinal absorption of active drug and only lung absorption, what is the L/T ratio?
Answer: 1; $\text{L/T} \equiv \text{lung availability} / (\text{lung} + \text{stomach availability})$; and $\text{stomach} \equiv 0$.

6. True or False: A patient uses a reservoir device with an inhaled aerosol, and there is no swallowed portion of the drug; therefore there are no systemic side effects.

Answer: False. Systemic drug levels are caused by *total* drug absorbed from the gastrointestinal tract and lungs. Sufficient lung absorption of the active drug could produce extrapulmonary side effects.

7. Which receptor system signal mechanism is responsible for the effects caused by β -receptor activation, such as those seen with adrenergic bronchodilators (e.g., albuterol)?

Answer: G protein-linked receptors.

Clinical Scenario

Subjective: A 67-year-old man with a history of chronic obstructive pulmonary disease (COPD) hospitalized for a respiratory infection. An aerosol treatment of racemic epinephrine four times daily (qid) is ordered.

Objective: After the aerosol treatment, his heart rate (HR) decreased from 26 to 18 breaths/min. Adequate breath sounds were auscultated with a decrease in wheezing. It is noted that accessory muscle use has lessened and shortness of breath has been reduced after treatment at 8:00 AM. At 10:00 AM, accessory muscle use, wheezing, and shortness of breath return.

Assessment: After reviewing the pharmacokinetics of the drug, it is not suitable for a qid schedule. The duration of the drug's effect is too short. The improvement in airway resistance has declined, and the patient is working harder to breathe again.

Plan: You could administer racemic epinephrine more frequently, on a q2h (every 2 hours) schedule instead of the qid schedule. However, a better choice might be to identify a longer-acting bronchodilator with a duration of 4 to 6 hours, such as albuterol or levalbuterol. Both are noncatecholamine agents (see [Chapter 6](#)) that could be used in a qid schedule. Less frequent dosing is also more cost effective for an in-hospital patient.

Chapter 3

Self-Assessment Questions

1. What are the three most common aerosol-generating devices used to deliver inhaled drugs?

Answer: Small volume nebulizer (SVN), metered dose inhaler (MDI) with or without a reservoir device, and dry powder inhaler (DPI).

2. Describe the inspiratory pattern you would instruct a patient to use with an MDI.

Answer: Exhale to end-tidal volume; begin to inhale slowly through the mouth and simultaneously actuate the MDI; continue to inhale to total lung capacity and hold the breath for 5 to 10 seconds.

3. What are three advantages offered with use of a reservoir device with an MDI?

Answer: Reservoir devices can modify the aerosol plume from an MDI in three ways: (1) They allow time/distance between actuation and inhalation for particle evaporation and reduced particle size; (2) allow distance for the high initial particle velocity to slow; and (3) somewhat simplify the hand-breathing coordination required with MDI use. The net effect of the first two influences reduces oropharyngeal impaction and loss.

4. Would a DPI be appropriate for a 3-year-old child with asthma?

Answer: No. These devices require an inspiratory flow rate of 60 L/min or more for optimal use. This probably exceeds the capability of most 3-year-old children. DPIs are not recommended for children younger than 5 years.

5. What is meant by the term *dead volume* in an SVN?

Answer: Dead volume is the residual amount of solution left in a nebulizer when the nebulizer “sputters” and is no longer able to generate aerosol. This is usually around 0.5 to 1 mL in most disposable nebulizers.

6. What are the optimal filling volume and power gas flow rate to use with an SVN?

Answer: For most disposable nebulizers, the optimal filling volume is 3 to 5 mL and the power gas flow rate is 8 to 10 L/min. A flow rate of 8 L/min probably gives the maximal particle size penetration into the lower respiratory tract and therefore produces the maximal drug mass able to reach the airway. However, a flow rate of 10 L/min will reduce particle size further and decrease the treatment time.

7. How does the electrostatic charge affect an MDI when used with a holding chamber?

Answer: The electrostatic charge pulls the particles out of suspension, thereby decreasing the amount of drug available to the patient. At present, some manufacturers produce “anti-static” chambers; however, it has been found that washing a standard holding chamber with household detergent and allowing it to air dry will decrease the static. Decreasing static increases the available drug to the patient.

8. Which device would be better to deliver a β agonist to an adult patient in the emergency department (ED)—SVN, MDI, or DPI?

Answer: It really depends on a number of factors, including drug availability, patient or clinical preference, practicality, and convenience. The best choice would be an SVN or MDI with a holding chamber. An MDI without a holding chamber or a DPI would not be good selections because of the patient not being able to coordinate and decreased inspiratory flow.

Clinical Scenario

Subjective: A 17-year-old adolescent male with a history of allergic asthma complains that he can feel drug in the canister when he shakes it before using, but it feels as if “very little spray” is coming out when he inhales a puff. He believes the MDI is not functioning properly and that he is not getting the regular inhaled dose.

Objective: Not available.

Assessment: Check MDI for correct use and educate patient on correct MDI use.

Plan: First check to be sure there are in fact no obstructions in the mouthpiece of the actuator. After shaking well, discharge a dose to room air (away from everyone) to see whether there is a visible plume. If possible, you might compare the aerosol plume from his canister with another MDI to see whether they appear comparable. If you have a laboratory (i.e., in the hospital), try to have the canister weighed to ensure adequate fullness. Short of analyzing the aerosol, you cannot guarantee a correct dose of albuterol, but you can measure the person's peak expiratory flow with a peak flow meter or his forced expiratory volume in 1 second (FEV₁) with a portable spirometry screening unit before and after use. If he exhibits his usual amount of reversibility, this is indirect evidence of drug delivery. Also, ask him if he obtains relief when he uses the MDI during wheezing or chest tightness.

The HFA formulation of albuterol has a higher plume temperature and a lower plume force on actuation. It is a softer and gentler spray. Patients who may have used a chlorofluorocarbon (CFC) formulation of albuterol by MDI often think they are not getting the usual dose because they cannot feel the colder, forceful blast they experienced with the CFC formulation.

Chapter 4

Self-Assessment Questions

Prepared-Strength Dose Calculations

1. A bottle is labeled Demerol (meperidine) 50 mg/cc. How many cubic centimeters are needed to give a 125-mg dose?
Answer: $50 \text{ mg}/1 \text{ cc} \equiv 125 \text{ mg}/x \text{ cc}; x \equiv 2.5 \text{ cc}$.
2. An agent comes as 500 mg/10 mL. How many milliliters are needed to give a 150-mg dose?
Answer: $500 \text{ mg}/10 \text{ mL} \equiv 150 \text{ mg}/x \text{ mL}; x \equiv 3 \text{ mL}$.
3. Hyaluronidase comes as 150 U/cc. How many cubic centimeters are needed for a 30-U dose?
Answer: $150 \text{ U}/\text{cc} \equiv 30 \text{ U}/x \text{ cc}; x \equiv 0.2 \text{ cc}$.
4. Morphine sulfate 4 mg is ordered; you have a vial with 10 mg/mL. How much do you need?
Answer: $10 \text{ mg}/\text{mL} \equiv 4 \text{ mg}/x \text{ mL}; x \equiv 0.4 \text{ mL}$.
5. A dosage schedule for the surfactant poractant calls for an infant with a 2.5 mL/kg birth weight. How much of the drug will you need for an infant weighing 800 g?
Answer: $800 \text{ g} \times 1 \text{ kg}/1000 \text{ g} \equiv 0.8 \text{ kg}; 2.5 \text{ mL}/\text{kg} \times 0.8 \text{ kg} \equiv 2 \text{ mL}$.
6. Diphenhydramine (Benadryl) elixir contains 12.5 mg of diphenhydramine HCl in each 5 mL of elixir. How many milligrams are there in a $\frac{1}{2}$ teaspoonful dose (1 tsp $\equiv$ 5 mL)?
Answer: $\frac{1}{2} \text{ teaspoon} \equiv 2.5 \text{ mL}$.
 $12.5 \text{ mg}/5 \text{ mL} \equiv x \text{ mg}/2.5 \text{ mL}; x \equiv 6.25 \text{ mg}$.
7. A pediatric dose of 100 mg of a syrup is ordered. The dosage form is an oral suspension containing 125 mg/5 cc. How much of the suspension contains a 100-mg dose?
Answer: $125 \text{ mg}/5 \text{ cc} \equiv 100 \text{ mg}/x \text{ cc}; x \equiv 4 \text{ cc}$.
8. How many units of heparin are found in 0.2 mL, if you have 1000 U/mL?
Answer: $1000 \text{ U}/\text{mL} \equiv x \text{ units}/0.2 \text{ mL}; x \equiv 200 \text{ U}$.
9. Albuterol syrup is available as 2 mg/5 mL. If a dosage schedule of 0.1 mg/kg is used, how much syrup is needed for a 30-kg child? How many teaspoons is this?
Answer: $30 \text{ kg} \times 0.1 \text{ mg}/\text{kg} \equiv 3 \text{ mg}$
 $2 \text{ mg}/5 \text{ mL} \equiv 3 \text{ mg}/x \text{ mL}; x \equiv 7.5 \text{ mL}$
 $7.5 \text{ mL} \times 1 \text{ tsp}/5 \text{ mL} \equiv 1.5 \text{ tsp}$
10. Terbutaline is available as 2.5-mg tablets. How many tablets do you need for a 5-mg dose?
Answer: $2.5 \text{ mg}/1 \text{ tab} \equiv 5 \text{ mg}/x \text{ tab}; x \equiv 2 \text{ tablets}$.
11. If a cough syrup is available as 120 mg/5 mL, how much of the drug is there in $\frac{1}{2}$ tsp?
Answer: $\frac{1}{2} \text{ tsp} \equiv 2.5 \text{ mL}; 120 \text{ mg}/5 \text{ mL} \equiv x \text{ mg}/2.5 \text{ mL}; x \equiv 60 \text{ mg}$.
12. Theophylline is available as 250 mg/10 mL and is given intravenously at 6 mg/kg body weight. How much solution do you give to a 60-kg woman?
Answer: $60 \text{ kg} \times 6 \text{ mg}/\text{kg} \equiv 360 \text{ mg}; 250 \text{ mg}/10 \text{ mL} \equiv 360 \text{ mg}/x \text{ mL}; x \equiv 14.4 \text{ mL}$.
13. Terbutaline sulfate is available as 1 mg/mL in an ampule. How many milliliters are needed for a 0.25-mg dose?
Answer: $1 \text{ mg}/\text{mL} \equiv 0.25 \text{ mg}/x \text{ mL}; x \equiv 0.25 \text{ mL}$.
14. A patient is told to take 4 mg of albuterol four times daily. The medication comes in 2-mg tablets. How many tablets are needed for one 4-mg dose?
Answer: $2 \text{ mg}/\text{tab} \equiv 4 \text{ mg}/x \text{ tab}; x \equiv 2 \text{ tablets}$.
15. An agent is available as a syrup with 10 mg/5 mL. How many teaspoons should be taken for a 20-mg dose?
Answer: $1 \text{ tsp} \equiv 5 \text{ mL}$.
 $10 \text{ mg}/5 \text{ mL} \equiv 20 \text{ mg}/x \text{ mL}; x \equiv 10 \text{ mL}$.
 $10 \text{ mg} \times 1 \text{ tsp}/5 \text{ mL} \equiv 2 \text{ tsp}$.
16. If an agent is available at 3 mg/mL, how many milliliters are needed for a dose of 9 mg?
Answer: $3 \text{ mg}/\text{mL} \equiv 9 \text{ mg}/x \text{ mL}; x \equiv 3 \text{ mL}$.
17. If a dosage schedule requires 0.25 mg/kg of body weight, what dosage is needed for an 88-kg person?
Answer: $0.25 \text{ mg}/\text{kg} \times 88 \text{ kg} \equiv 22 \text{ mg}$.
18. If theophylline is available as 80 mg/15 mL, how much is needed for a 100-mg dose?
Answer: $80 \text{ mg}/15 \text{ mL} \equiv 100 \text{ mg}/x \text{ mL}; x \equiv 18.75 \text{ mL}$.
19. How much of a drug is needed for a 65-kg adult, using 0.5 mg/kg?
Answer: $0.5 \text{ mg}/\text{kg} \times 65 \text{ kg} \equiv 32.5 \text{ mg}$.
20. The pediatric dosage of an antibiotic is 0.5-g/20-lb body weight, not to exceed 75 mg/kg/24 hr.
 - a. What is the dose for a 40-lb child?
 - b. If this dose is given twice in 1 day, has the maximal dose been exceeded?*Answers:*
 a. $0.5 \text{ g}/20 \text{ lb} \times 40 \text{ lb} \equiv 1.0 \text{ g}$.
 b. $2 \text{ doses} \equiv 2 \times 1.0 \text{ g} \equiv 2.0 \text{ g} \equiv 2000 \text{ mg}$
 $40 \text{ lb} \times 1 \text{ kg}/2.2 \text{ lb} \equiv 18 \text{ kg}$
 $2000 \text{ mg}/18 \text{ kg} \equiv 111.1 \text{ mg}/\text{kg}$
 Yes, the maximal dose has been exceeded: two doses give 2000 mg/40 lb, which is 2000 mg/18 kg, or 111.1 mg/kg/day.

Percent-Strength Solutions

1. How many grams of calamine are needed to prepare 120 g of an ointment containing 8% calamine?
Answer: $0.08 \equiv x \text{ g}/120 \text{ g}; x \equiv 9.6 \text{ g}$.
2. In 147 mL of solution, there is 1 mL of active enzyme. What is the percent strength of active enzyme in the solution?
Answer: $x \equiv 1 \text{ mL}/147 \text{ mL}; x \equiv 0.0068 \equiv 0.68\%$.
3. If theophylline is available in a 250 mg/10 mL solution, what percent strength is this?
Answer: $x \equiv 0.25 \text{ g}/10 \text{ mL}; x \equiv 0.025 \equiv 2.5\%$.
4. You have epinephrine 1:100. How many milliliters of epinephrine would be needed to contain 30 mg of active ingredient?
Answer: $0.01 \equiv 0.03 \text{ g}/x \text{ mL}; x \equiv 3 \text{ mL}$.
5. A dose of 0.4 mL of epinephrine HCl 1:100 is ordered. This dose contains how many milligrams of epinephrine HCl (the active ingredient)?
Answer: $0.01 \equiv x \text{ g}/0.4 \text{ mL}; x \equiv 0.004 \text{ g} \equiv 4 \text{ mg}$.
6. If you administer 3 mL of a 0.1% strength solution, how many milligrams of active ingredient have you given?
Answer: $0.001 \equiv x \text{ g}/3 \text{ mL}; x \equiv 0.003 \text{ g} \equiv 3 \text{ mg}$.
7. A drug is available as a 1:200 solution, and the maximal dose that may be given by aerosol for a particular patient is 3 mg. What is the maximal amount of solution (in milliliters) that may be used?
Answer: $1:200 \equiv 0.5\% \equiv 0.005; 3 \text{ mg} \equiv 0.003 \text{ g}; 0.005 \equiv 0.003 \text{ g}/x \text{ mL}; x \equiv 0.6 \text{ mL}$.

8. Epinephrine 1:1000 contains how many milligrams of active ingredient per milliliter?
Answer: $1:1000 \equiv 0.1\% \equiv 0.001$; $0.001 \equiv x \text{ g/1 mL}$; $x \equiv 0.001 \text{ g} \equiv 1 \text{ mg}$.
9. How many milligrams per milliliter are there in 0.3 mL of a 5% strength agent?
Answer: $0.05 \equiv x \text{ g/0.3 mL}$; $x \equiv 0.015 \text{ g} \equiv 15 \text{ mg}$.
10. How many milligrams of sodium chloride are needed for 10 mL of a 0.9% solution?
Answer: $0.009 \equiv x \text{ g/10 mL}$; $x \equiv 0.09 \text{ g} \equiv 90 \text{ mg}$.
11. If you have lidocaine (Xylocaine) at 5 mg/mL, what percent strength is it?
Answer: $x \equiv 0.005 \text{ g/mL}$; $x \equiv 0.005 \equiv 0.5\%$.
12. A 0.5% strength solution contains how many milligrams in 1 mL?
Answer: $0.005 \equiv x \text{ g/mL}$; $x \equiv 0.005 \text{ g} \equiv 5 \text{ mg}$.
13. Cromolyn sodium contains 20 mg in 2 mL of water. What is the percent strength?
Answer: $x \equiv 0.02 \text{ g/2 mL}$; $x \equiv 0.01 \equiv 1\%$.
14. How much active ingredient of acetylcysteine have you given with 4 cc of a 20% solution?
Answer: $0.2 \equiv x \text{ g/4 cc}$; $x \equiv 0.8 \text{ g} \equiv 800 \text{ mg}$.
15. You have 20% acetylcysteine; how many milliliters of this do you need to form 4 mL of an 8% solution?
Answer: $0.08 \equiv 0.2(x) \text{ mL/4 mL}$; $0.2(x) \equiv 0.32$; $x \equiv 1.6 \text{ mL}$, and saline qs (as required) for 4 mL.
16. The recommended dose of an agent with a percent strength of 5% is 0.3 cc. How many milligrams of solute are there in this amount?
Answer: $0.05 \equiv x \text{ g/0.3 cc}$; $x \equiv 0.015 \text{ g} \equiv 15 \text{ mg}$.
17. Acetylcysteine was marketed as 10% acetylcysteine with 0.05% isoproterenol. How many milligrams of each ingredient were in a 4-cc dose of solution? (Isoproterenol: $0.0005 = x \text{ g/4 cc}$; $x = 0.002 \text{ g} = 2 \text{ mg}$)
Answer: Acetylcysteine: $0.10 \equiv x \text{ g/4 cc}$; $x \equiv 0.4 \text{ g} \equiv 400 \text{ mg}$.
18. Which contains more drug: $\frac{1}{2}$ cc of a 1% drug solution with 2 mL of saline or $\frac{1}{2}$ of a 1% drug solution with 5 mL of saline?
Answer: They each contain the same amount of drug: 5 mg ($0.01 \equiv x \text{ g/0.5 cc}$; $x \equiv 0.005 \text{ g} \equiv 5 \text{ mg}$). The different amounts of diluent (2 mL, 5 mL) will change the resulting percentage strength and the total amount of new solution but not the amount of drug.
19. How many milligrams per milliliter are in a 20% solution?
Answer: $0.20 \equiv x \text{ g/mL}$; $x \equiv 0.2 \text{ g} \equiv 200 \text{ mg}$.

Clinical Scenario

You have a 1 normal (N) solution of saline (NaCl) and you need isotonic saline 0.9%, also called “normal saline,” for diluent in a nebulizer solution. *Can you use the 1 N solution as diluent, unchanged?*

Answer: A 1 normal (N) solution contains 1 g equivalent weight (GEW) of solute per liter of solution. If we calculate the percentage strength of a 1 N solution of NaCl, we can compare this with 0.9% to determine equivalence or lack of equivalence. The molecular weights of sodium (Na) and chlorine (Cl) are 23 and 35.5, respectively. A GEW is the molecular weight divided by the valence of the elements:

1 GEW, NaCl $\equiv 23.0 \text{ g} + 35.5 \text{ g} \equiv 58.5 \text{ g}$. 1 N solution $\equiv 1 \text{ GEW/L} \equiv 58.5 \text{ g/L}$ or $5.85 \text{ g/100 mL} \equiv 5.85\%$.

Therefore, a 1 N solution of NaCl is 5.85% strength and is not the same concentration as normal saline, which is 0.9% strength. A 0.9% solution would be 0.9 g/100 mL, not 5.85 g/100 mL. Use of the more concentrated 1 N solution, which is hypertonic relative to body fluid, may cause bronchial irritation in a nebulizer solution for inhalation.

Chapter 5

Self-Assessment Questions

1. Which portion of the nervous system is under voluntary control: the autonomic or the skeletal muscle motor nerve portion?
Answer: The skeletal muscle motor nerve portion.
2. What is the neurotransmitter at each of the following sites—neuromuscular junction; autonomic ganglia; and most sympathetic end sites?
Answer: Neuromuscular junction—acetylcholine; autonomic ganglia—acetylcholine; most sympathetic end sites—norepinephrine.
3. Where are muscarinic receptors found?
Answer: At parasympathetic nerve terminal sites.
4. What is the effect of cholinergic stimulation on airway smooth muscle?
Answer: Bronchoconstriction.
5. What is the effect of adrenergic stimulation on the heart?
Answer: Increased rate and force of contraction.
6. Classify the drugs pilocarpine, physostigmine, propranolol, and epinephrine.
Answer: Pilocarpine—direct-acting cholinergic; physostigmine—indirect-acting cholinergic; propranolol—adrenergic-blocking agent (β_1 and β_2); epinephrine—adrenergic agonist (stimulates α and β receptors).
7. How do indirect-acting cholinergic agonists (parasympathomimetics) produce their action?
Answer: Indirect-acting parasympathomimetics, such as neostigmine, inhibit the enzyme cholinesterase, which increases the amount of acetylcholine available to stimulate postsynaptic sites at the nerve terminal.
8. What effect would the drug atropine have on the eye and on airway smooth muscle?
Answer: Atropine is a competitive blocking agent for muscarinic receptors. The drug would block the eye circular iris muscle to dilate the pupil (mydriasis), paralyze the ciliary muscle to flatten the lens (cycloplegia), and antagonize cholinergically induced bronchoconstriction in the airway.
9. What is the general difference between α and β receptors in the sympathetic nervous system?
Answer: The α receptors generally cause an excitatory effect (e.g., vasoconstriction), and β receptors generally produce inhibition (e.g., airway smooth muscle relaxation).
10. What is the primary mechanism for terminating the neurotransmitters acetylcholine and norepinephrine?
Answer: Acetylcholine is metabolized by cholinesterase enzymes; norepinephrine is reabsorbed back into the presynaptic neuron.
11. What is the predominant sympathetic receptor type found on airway smooth muscle?
Answer: The β_2 receptor.
12. Identify the adrenergic receptor preference for phenylephrine, norepinephrine, and epinephrine.

Answer: Phenylephrine— α receptors (α_1 specifically); norepinephrine— $\alpha > \beta$ receptors; epinephrine— α and β receptors equally.

13. What is the autoregulatory receptor on the sympathetic presynaptic neuron?

Answer: α_2 Receptors.

14. Classify the following drugs by autonomic class and receptor preference: dopamine, ephedrine, albuterol, phentolamine, propranolol, and prazosin.

Answer: Dopamine—sympathomimetic (dopamine receptors, α , and β); ephedrine—sympathomimetic (α and β); albuterol—sympathomimetic (β_2 preferential); phentolamine—sympatholytic (α_1 and α_2); propranolol— β sympatholytic (β_1 and β_2); prazosin— α_1 sympatholytic.

15. What is the autoregulatory receptor on the parasympathetic presynaptic neuron at the terminal nerve site?

Answer: The muscarinic receptor subtype M_2 .

16. Contrast general, α_1 -receptor and α_2 -receptor effects.

Answer: α_1 -Receptor effects are generally excitatory (e.g., vasoconstriction of peripheral blood vessels). α_2 -Receptor effects are generally inhibitory (e.g., inhibition of norepinephrine release from nerve terminals).

17. What substance may be the neurotransmitter in the NANC inhibitory nervous system in the lung?

Answer: Vasoactive intestinal peptide (VIP) or possibly nitric oxide (NO).

18. What substance is the neurotransmitter in the NANC excitatory nervous system in the lung?

Answer: Substance P.

Clinical Scenario

Subjective: A 42-year-old white female with a long-standing history of asthma presents to the ED. She states that she has been feeling as if her “heart was racing” today. She currently uses a β -adrenergic bronchodilator (albuterol), as needed, and inhales an anticholinergic bronchodilator (ipratropium bromide) before bedtime.

Objective: On admission to the ED, she has the following vital signs: pulse (P), 155 beats/min and regular; blood pressure (BP), 146/90 mm Hg; and respiratory rate (RR), 22 breaths/min, with mild distress. Her breath sounds are clear to auscultation and a chest radiograph (posteroanterior [PA]) shows no abnormalities. A lead II electrocardiogram reveals supraventricular tachycardia (SVT). Oxygen saturation as revealed by pulse oximetry (saturation of peripheral oxygen [SpO_2]) is 90%.

Assessment: This is an example of altering the balance of autonomic control in the lung. Propranolol (Inderal) is a nonspecific β blocker (β_1 and β_2). As a β_1 -blocking agent the drug will slow heart rate. However, the blockade of β_2 receptors in the airway prevents endogenous epinephrine and exogenous adrenergic agents from stimulating those receptors. The IV dose directly antagonizes the effect of the β -receptor stimulation in the airways with the adrenergic bronchodilator albuterol, and it inhibits the degree of bronchodilation achieved in this patient with asthma, whose airways tend to react to stimuli and constrict. The balance between adrenergic relaxation of the airway and cholinergic constriction is tipped in favor of unbalanced cholinergic activity. She begins to exhibit symptoms of bronchoconstriction (wheezing, dyspnea).

Plan: Prevention is the best approach. In a patient, such as one with asthma, β -receptor stimulation is an important property to preserve. The use of a drug other than a β -blocking agent

would be indicated for the supraventricular tachycardia (SVT) to avoid the undesirable side effect of β blockade in the lung. Alternative drugs for tachycardia are discussed in subsequent chapters; these would include a calcium channel-blocking agent, such as verapamil, or an agent such as amlodipine. Her use of the β -adrenergic bronchodilator albuterol, which is a β_2 agonist, should also be reviewed to ensure proper dosage and frequency of use. Although it is β_2 specific, an adrenergic agonist can stimulate the heart.

Chapter 6

Self-Assessment Questions

1. Identify an adrenergic bronchodilator used clinically that is a catecholamine.

Answer: Racemic epinephrine.

2. Which catecholamine has been used as a bronchodilator and is commonly given to treat allergic reaction by self-injection?

Answer: Epinephrine.

3. What is the duration of action of the catecholamine bronchodilators?

Answer: Approximately 1.5 hours; up to 3 hours at most.

4. Identify two advantages introduced with the modifications of the catecholamine structure in adrenergic bronchodilators.

Answer: Increased β_2 specificity and longer duration of action.

5. Identify the usual dose by aerosol for a small volume nebulizer (SVN) for levalbuterol and albuterol.

Answer: Levalbuterol—0.63 to 1.25 mg; albuterol—0.5 cc of a 0.5% concentration.

6. What is an extremely common side effect with β_2 -adrenergic bronchodilators?

Answer: Muscle tremor.

7. Identify the approximate duration of action for racemic epinephrine, albuterol, salmeterol, and olodaterol.

Answer: Racemic epinephrine—1 to 3 hours; albuterol—4 to 6 hours; salmeterol—12 hours; olodaterol—24 hours.

8. Identify the generic drug for each of the following brand names: Brovana, Serevent Diskus, and Ventolin HFA.

Answer: Brovana—arformoterol; Serevent Diskus—salmeterol; and Ventolin HFA—albuterol.

9. Which route of administration is more likely to have greater severity of side effects with a β -agonist, oral or inhaled aerosol?

Answer: Oral (tremor is more severe).

10. You notice a pinkish tinge to aerosol rainout in the large-bore tubing connecting a patient's mouthpiece to a nebulizer after a treatment with racemic epinephrine; what has caused this?

Answer: The catecholamine epinephrine will be broken down by light and air to the adrenochrome form, producing a pinkish or pinkish-brown residue in tubing.

11. A patient exhibits paradoxical bronchoconstriction from the propellant when using a hydrofluoroalkane metered dose inhaler (HFA MDI). Suggest an alternative for the patient.

Answer: Consider trying the liquid formulation, DPI, or a RespiMat depending on availability of the drugs and devices.

12. Would you suggest use of salmeterol to a patient with asthma who experiences occasional symptoms of wheezing and chest tightness, which respond well to an inhaled β agonist?

Answer: No; salmeterol is indicated for maintenance therapy in patients with asthma needing regular use of a β agonist

(regular β agonist and inhaled corticosteroid or other agents); it also should be used in conjunction with an inhaled corticosteroid.

13. Suggest a β agonist that would be appropriate for the patient in question 12.

Answer: Any of the following: albuterol or levalbuterol.

Clinical Scenario

Subjective: A 24-year-old White male presents with the complaint of difficulty breathing. He has no history of asthma or other previous pulmonary disease. He is an accountant with a medium-size firm. He noticed a few “chest colds” from October through January, but these resolved with over-the-counter cold medications, such as decongestants and cough suppressants. During a round of golf in late May, he had difficulty breathing. On interview, he described tightness in his chest and the sound of wheezing. The course had recently been mown. The pollen count was quite high at the time, and there was an increased ozone concentration, leading to a smog alert on the day of his round. He also complained of waking up several times during the night with mild shortness of breath.

Objective: His respiratory rate (RR) is 14 breaths/min with no obvious distress at rest; blood pressure (BP) is 128/74 mm Hg; heart rate (HR) is 76 beats/min; and temperature (T) is within normal limits. His oxygen saturation by pulse oximetry (SpO_2) is 93% on room air. On auscultation you detect mild expiratory wheezing bilaterally.

Assessment: Asthma exacerbation.

Plan: Administer a peak flow. Alternatively, office spirometry would provide more complete information on his FEV_1 and midmaximal flow rates. A “before and after” bronchodilator study would further determine whether he has *reversible* obstruction; however, his history and symptoms suggest this. If low, treatment with a short-acting bronchodilator, such as albuterol or levalbuterol, would be appropriate. Because he will be going home, an HFA MDI would be best. Correct education on its use is a must.

Answer: Maintenance treatment of COPD.

6. Which disease state—asthma or COPD—may show greater response to an anticholinergic bronchodilator rather than a β agonist?

Answer: COPD patients are likely to have a greater response to an anticholinergic agent rather than a β agonist in reversibility of airflow obstruction.

7. With which type of anticholinergic agent are you more likely to observe systemic side effects: tertiary ammonium or quaternary ammonium compounds?

Answer: Tertiary; these are less ionized and are better absorbed and distributed through body tissues.

8. What are the most common side effects seen with inhaled ipratropium and tiotropium?

Answer: Dry mouth and cough.

9. Can ipratropium be used with patients who have glaucoma?

Answer: Yes. However, use with caution, have the patient notify his or her ophthalmologist, and monitor intraocular pressures.

10. Can ipratropium be alternated with or combined with a β agonist in the treatment of COPD and asthma?

Answer: Yes. The two types of agents may have additive effects in reversing airflow obstruction. In addition, they have complementary sites and mechanisms of action, and the time to peak effect is later for ipratropium compared with that of a β agonist, resulting in more sustained peak bronchodilation.

11. What precautions should you observe if administering ipratropium by SVN?

Answer: Protect the eyes from exposure to the nebulized drug by using a mouthpiece instead of a mask whenever possible or covering the eyes if a facemask is used for administration. This is done to avoid the ocular effects of mydriasis and cycloplegia.

12. What is the clinical indication for the use of an anticholinergic intranasal spray?

Answer: Rhinorrhea associated with nonallergic perennial rhinitis, colds, and allergic rhinitis if unresponsive to intranasal corticosteroids.

Chapter 7

Self-Assessment Questions

1. What was the first FDA-approved anticholinergic bronchodilator for aerosol inhalation?

Answer: Ipratropium (Atrovent).

2. List all FDA-approved long-acting anticholinergic combination product(s) on the market.

Answer: Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, and Stiolto Respimat

3. What is the usual recommended dose of ipratropium by MDI and by SVN?

Answer: MDI—34 mcg, two actuations, each 17 mcg (from the mouthpiece). SVN—500 mcg, 2.5 mL of a 0.02% solution.

4. Identify a long-acting anticholinergic bronchodilator and give its duration of action.

Answer: Tiotropium (Spiriva), aclidinium (Tudorza Pressair), umeclidinium (Incruse Ellipta) and revefenacin (Yupelri); all up to 24 hours.

5. What is the usual clinical indication for use of an anticholinergic bronchodilator, such as ipratropium?

Clinical Scenario

Subjective: On interview, he states that he has increasingly noticed exertional dyspnea with mild physical activity over the past few months. With questioning, he admits to occasional social alcohol intake of one or two beers or a couple of mixed drinks several times a week. He has been happily married to the same woman since he was 24 years of age. He also admits to regular cigarette smoking of about 1 pack/day since he was 20 years of age. He leads a sedentary life with no physical exercise. He states that he does have a chronic cough, which is worse in the morning, although he denies much productivity.

Objective: Physical examination reveals very mild digital clubbing, a slightly increased anteroposterior (AP) diameter, diminished and distant breath sounds bilaterally with some rhonchi, mildly hyperresonant percussion notes, no jugular venous distention upright or supine, and no peripheral edema. His vital signs are as follows: blood pressure (BP), 146/90 mm Hg; temperature (T), 99°F; pulse (P), 88 beats/min; and respiratory rate (RR), 16 breaths/min with no laboring. His arterial blood gas (ABG; room air) results are as follows: pH, 7.40; arterial

carbon dioxide pressure (PaCO_2), 42.5 mm Hg; arterial oxygen pressure (PaO_2), 62 mm Hg; base excess, 1.9 mEq/L; and hemoglobin (Hgb), 14.5 g/dL. Chest radiograph (PA, lateral) shows some loss of lung markings, mild flattening of the hemidiaphragms, and increased AP diameter. His electrolytes and white blood cell (WBC) count are normal. Moderate airflow obstruction is present, as evidenced by the FEV_1 of 1.94 L, an FEV_1/FVC of 65%, and an increased residual volume/total lung capacity (RV/TLC) ratio. Gas exchange is impaired, as seen in the below-normal diffusing capacity of the lungs for carbon monoxide (DL_{CO}).

Assessment: COPD, probably bronchitis and emphysema.

Plan: First and foremost, the patient should quit smoking. Give smoking cessation material and program information to him. Second, consider a rehabilitation or disease management educational program to incorporate knowledge of the disease, its treatment options, exercise, and nutrition. A bronchodilator should be considered after assessing the degree of reversibility of his airflow obstruction by spirometry after bronchodilator administration. Furthermore, the use of both a β agonist and anticholinergic may be warranted. If the postassessment of spirometry is positive, a short- β agonist should be prescribed on an as-needed basis. More notable would be to place the patient on a long-acting β -agonist and anticholinergic. The addition of “triple” therapy may also be considered.

Chapter 8

Self-Assessment Questions

1. What drug in the xanthine group is used most often therapeutically?
Answer: Theophylline.
2. In which formulations is theophylline available?
Answer: Tablets, capsules, syrup, elixir, extended-release tablets, capsules, injection.
3. What is the recommended therapeutic plasma level for theophylline in asthma and COPD?
Answer: 5 to 15 mcg/mL, asthma; 5 to 10 mcg/mL, COPD.
4. How do you know whether a given dose of theophylline would produce a satisfactory treatment effect in a patient with asthma?
Answer: The most exact method is to monitor the plasma level of theophylline and adjust the dose to maintain a therapeutic plasma level. Alternatively, and less precisely, the dose can be adjusted to control symptoms and side effects.
5. Identify at least three adverse side effects seen with theophylline.
Answer: Gastric irritation, insomnia, anxiety/shakiness, tachycardia, nausea, loss of appetite, and headache.
6. What is meant by a “narrow therapeutic margin”?
Answer: For a drug with a narrow therapeutic margin, the dose required to produce a therapeutic effect is close to the dose that begins to produce toxic side effects.
7. Although theophylline is a weak bronchodilator, what other effects make it useful in treating chronic airflow obstruction?
Answer: (1) Stimulation of ventilatory drive in the central nervous system and (2) strengthening of diaphragmatic contractile force.
8. True or False: Theophylline causes bronchodilation and improved airflow solely by inhibiting phosphodiesterase, which breaks down cAMP.
Answer: False. The mechanism of action of theophylline is unclear.

Clinical Scenario

Subjective: A 70-year-old White male arrived to the hospital ED complaining of dyspnea. He reported coughing up thick, greenish sputum with some tinges of blood in the last few days. In the interview, he admitted to smoking two packs of cigarettes a day since age 18 years, stopping about 2 years ago. He has had six hospitalizations within the last 2 years. Current medications include ipratropium bromide by MDI, 2 puffs four times daily, with a β_2 agonist by MDI as needed, 1 to 3 puffs. He reports he has been using the β_2 MDI regularly during the last month, at least four times daily.

Objective: On physical examination, he was very short of breath (SOB), even at rest, and used accessory muscles with a respiratory rate (RR) of 22 breaths/min. There was little discernible chest expansion. His breath sounds were distant in all areas with expiratory wheezes and air movement appeared poor. He was afebrile with a pulse (P) of 120 beats/min and blood pressure (BP) of 170/112 mm Hg. He appeared oriented, coherent, and somewhat malnourished, with thin arms. Laboratory values on admission showed normal electrolytes, but his white blood cell (WBC) count was $15.2 \times 10^3/\text{cc}$ and his hemoglobin was 10.6 g/dL. Arterial blood gas (ABG) values on room air were as follows: pH, 7.40; arterial carbon dioxide pressure (PaCO_2), 42.4 mm Hg; arterial oxygen pressure (PaO_2), 64 mm Hg; base excess, +1.9 mEq/L; and arterial oxygen saturation (Sao_2), 90%. A chest radiograph (posteroanterior [PA]) shows hyperinflation of the lung fields with flattened diaphragms.

Assessment: He has an exacerbation of COPD.

Plan: Administer oxygen. Although a PO_2 of 64 mm Hg on room air with a saturation of 90% appears to be satisfactory, this is achieved by a labored pattern of respiration with tachypnea (respiratory rate [RR], 22 breaths/min) and is accompanied by increased blood pressure (170/112 mm Hg) and tachycardia (120 beats/min). In addition, he is mildly anemic. Relieving his hypoxemia, and thereby reducing his work of breathing and myocardial work, may prevent the need for ventilatory support. Administer a short-acting β agonist and anticholinergic. Consider use of IV steroids with possible consideration of theophylline. After exacerbation is relieved, consider tiotropium bromide to replace ipratropium bromide at home.

Chapter 9

Self-Assessment Questions

1. Identify the mucolytic agents approved for inhalation as an aerosol in the United States—give the generic and brand names.
Answer: Dornase alfa (Pulmozyme), given 2.5 mg daily by jet nebulization; hypertonic (7%) saline, 4 mL by jet nebulization up to four times daily, and *N*-acetylcysteine (NAC; or Mucomyst), 4 mL of a 10% solution by jet nebulization (however, the latter is not of proven benefit for airway disease).
2. What is the mode of action for dornase alfa?
Answer: Depolymerizes extracellular DNA, decreasing sputum tenacity.
3. What is the clinical indication for use of dornase alfa?
Answer: To promote secretion clearance in persons with cystic fibrosis (CF).

4. What are contraindications to the use of mucolytic medications?

Answer: Poor or absent cough reflex, weakness, inability to protect the airway, and allergy or documented sensitivity to the medication used.

5. How do macrolide antibiotics affect mucus, and what are their indications for use?

Answer: Low-dose macrolide antibiotics are mucoregulatory medications that decrease mucus hypersecretion caused by inflammation and also preserve the normal or constitutive secretion.

6. How should dornase alfa be administered when high-frequency chest wall compression is used?

Answer: It may be at least as effective, and probably easier to administer, when given concomitant with high-frequency chest wall compression (HFCWC).

7. What is a common side effect seen with NAC by aerosol?

Answer: Bronchospasm, airway inflammation, and decreased pulmonary function.

8. What are the indications for the use of acetylcysteine?

Answer: Acetylcysteine is approved for systemic use in treating acetaminophen overdose. There are no indications for giving this as an aerosol.

9. How and when should bicarbonate aerosol or instillation be used?

Answer: It should not be used as a mucoactive drug.

Clinical Scenario

Subjective: A 17-year-old woman with CF was admitted to your hospital with an acute respiratory infection (pulmonary exacerbation). She is pleasant, mature, and well informed concerning her disease. She complains of an increased cough, increased sputum production with some hemoptysis, and weight loss over the past 2 weeks.

Objective: She was diagnosed with CF at the age of 2 years because of failure to thrive and did well clinically until age 12 years. She had a nasal polypectomy and a G-tube placed for night feeding several years ago, which resulted in a weight gain of 30 lb (13.6 kg). She is chronically infected with resistant *Pseudomonas* and *Stenotrophomonas*, and her culture results had demonstrated atypical *Mycobacterium* in the past. She has been admitted with exacerbations of CF twice in the past year. She has been taking 300 mg of tobramycin (TOBI) two times daily (bid) by aerosol at home regularly this year, with courses of oral ciprofloxacin when symptoms of respiratory infection surfaced. Vital signs are as follows: temperature (T), 99.5°F; pulse (P), 110 beats/min and regular; respiratory rate (RR), 26 breaths/min; and blood pressure (BP), 110/50 mm Hg. Oxygen saturation by pulse oximetry (SpO₂) is 0.92 in ambient air. She has mild dyspnea while walking. Auscultation of the chest revealed crackles in all fields, with more in the right upper lobe. Extremities showed clubbing with no cyanosis. She has a cough productive of greenish, thick sputum. No nasal polyps are visible to examination. Chest radiograph (posteroanterior [PA] and lateral) shows diffuse chronic changes with thick interstitial markings consistent with bronchiectasis, and a normal cardiac silhouette. There is an infiltrate in the right upper lobe. Her pulmonary function test results show a decrease in airflow and hyperinflation of the lung consistent with an obstructive disease state.

Assessment: Exacerbation of CF airway disease.

Plan: Her pulmonary function tests indicate moderate airway obstruction, accompanied by the usual problematic secretions

seen in CF. Her history also suggests increased bronchiectasis with purulent sputum production and a need for IV antibiotic therapy and hospitalization. She may benefit either from dornase alfa (Pulmozyme), 2.5 mg daily by nebulizer, or hyperosmolar (7%) saline. She may also find use of a β agonist, such as albuterol, helpful to improve or maintain lung function and secretion clearance. Finally, continued use of aerosolized antibiotic should be considered to reduce the bacterial burden of her respiratory secretions. Continue to assess the following to determine effectiveness of her dornase alfa treatment: (1) the use of parenteral antibiotics over the coming year; (2) the use of oral antibiotics over the next year; (3) the need for hospitalizations for acute exacerbations; and (4) maintenance or hopefully even improvement in her pulmonary function.

Chapter 10

Self-Assessment Questions

1. What is the definition of a *surface-active substance*?

Answer: An agent that can change surface tension at liquid–air interfaces.

2. In general, what is the clinical indication for use of exogenous surfactants?

Answer: Prevention (prophylaxis) of respiratory distress syndrome (RDS) in premature newborns with immature lungs or newborns with evidence of immature lung development, and treatment (rescue) of infants who have developed RDS

3. State the type (category) of exogenous surfactant for each of the following: beractant, calfactant, and poractant alfa.

Answer: Beractant (Survanta)—modified natural bovine extract; calfactant (Infasurf)—natural bovine extract; poractant alfa (Curosurf)—natural porcine extract.

4. What are the major ingredients of natural pulmonary surfactant?

Answer: Lipids (about 90%), including dipalmitoylphosphatidylcholine (DPPC); proteins, 10%.

5. Give the dosage schedule of each of the current exogenous surfactants.

Answer: Survanta—4 mL/kg; Infasurf—3 mL/kg; Curosurf—2.5 mL/kg.

6. What is the difference between “rescue” and “prophylaxis” treatment with surfactants?

Answer: Rescue—drug given in the presence of RDS. Prophylaxis—drug given *before* the onset of RDS.

7. Identify at least three possible adverse effects with the use of exogenous surfactant treatment.

Answer: Apnea, overventilation, overoxygenation, airway occlusion, desaturation, and bradycardia.

8. Why does the improvement in lung mechanics last after only one or two administrations of exogenous surfactant?

Answer: Apparently exogenous surfactant enters the recycling pool in alveolar cells.

9. How would you assess the effectiveness of exogenous surfactant treatment in a premature newborn with respiratory distress?

Answer: Monitor vital signs, including color and activity, for evidence of airway occlusion, desaturation, and bradycardia. Be prepared to manually ventilate and suction the airway. Assess changes in level of ventilation and oxygenation: chest rise, arterial oxygen saturation (SaO₂) or transcutaneous oxygen pressure (tcPO₂), exhaled volumes, and compliance. Modify ventilator settings and fraction of inspired oxygen (FiO₂) on the basis of changes.

Clinical Scenario

Subjective: A 16-year-old female gave birth to a 25-week, 515-g baby girl by vaginal delivery. The mother had no prenatal care and she had premature rupture of the membranes 12 days before delivery.

Objective: Apgar scores after intubation and application of positive-pressure ventilation with a bag and mask were 7 and 9 at 1 and 5 minutes, respectively. Physical examination revealed the following: pulse (P), 140 beats/min; blood pressure (BP), 34/22 mm Hg; temperature (T), 99.6°F; and oxygen saturation by pulse oximetry (SpO_2), 85% to 90%. Laboratory results revealed glucose, 39 mg/dL; white blood cell (WBC) count, 11,900/mm³; hematocrit, 47%; and platelets, 297,000/mm³. Chest radiograph showed respiratory distress syndrome, stage II.

Assessment: The gestational age and low birth weight indicate prematurity, which is associated with lung immaturity and lack of endogenous surfactant. The chest radiograph confirms the presence of neonatal RDS.

Plan: Administer an exogenous surfactant to the baby at the proper dose prescribed. Consider a second dose of surfactant if subsequent decline in lung function is indicated by the decrease in compliance, deteriorating vital signs, and oxygenation. Ventilation and oxygenation should be monitored after a repeat dose, and adjustments made to avoid overventilation and overoxygenation.

Chapter 11

Self-Assessment Questions

1. Identify all corticosteroids, using generic names approved in the United States for clinical use by oral inhalation.
Answer: Beclomethasone, fluticasone, budesonide, mometasone, and ciclesonide.
2. What is the major therapeutic effect of corticosteroids?
Answer: Their antiinflammatory effect.
3. Name two common respiratory diseases in which inhaled corticosteroids are prescribed.
Answer: Asthma and (less frequently) COPD.
4. What is the rationale for administering corticosteroids by the inhalation route, rather than by the oral route, in asthma?
Answer: By targeting the lung directly with corticosteroids that have high topical potency, systemic levels can be minimized and systemic side effects decreased or avoided.
5. Contrast the effects of β agonists with the effects of corticosteroids on the early phase and late phase of asthma.
Answer: β agonists may relieve the early phase of bronchoconstriction, whereas corticosteroids can reduce airway inflammation, preventing both the early and late phases of asthma.
6. What is the effect of orally administered corticosteroids on growth, bone density, and adrenal function?
Answer: Growth is decreased in children; bone density is decreased, causing osteoporosis; normal adrenal steroid secretion is suppressed, and in general the hypothalamic–pituitary–adrenal (HPA) axis activity is suppressed.
7. What is the purpose of alternate-day steroid therapy?
Answer: To reduce exposure of the body to exogenous corticosteroids and thereby reduce systemic side effects, such as adrenal suppression.

8. Can you switch from oral steroid use to inhaled steroid use in a patient with asthma? Explain the precautions or reasons, as appropriate.

Answer: Transfer can be accomplished; however, the patient should be weaned from the oral dose, using tapering doses while initiating inhaled steroids to allow adequate recovery of adrenal function because inhaled steroids will not maintain significant plasma levels at the recommended doses.

9. State two common side effects with inhaled steroids.
Answer: Oral thrush (candidiasis) and dysphonia.
10. Identify two methods of minimizing the side effects identified in question 9.
Answer: (1) Use of a reservoir device with MDI orally inhaled corticosteroids; (2) rinsing of the throat by gargling after inhaling a corticosteroid.
11. Have inhaled corticosteroids traditionally been used with an asthmatic during an acute episode?
Answer: No; there is no acute bronchodilating effect and the dose of inhaled steroids is too low for acute management of airway inflammation. However, inhaled corticosteroids have been investigated for ED treatment of acute severe asthma, along with aggressive bronchodilator therapy.

Clinical Scenario

Subjective: A 55-year-old White female presents to the ED with a chief complaint of cough, wheezing, shortness of breath, and chest pain. Two days earlier, she reported rhinorrhea, sore throat, sinus congestion, and subsequent increase in dyspnea and wheeze.

Objective: Physical examination on admission to the ED exhibited wheezing on auscultation, use of accessory muscles, no cyanosis or diaphoresis, and mild respiratory distress. Vital signs were as follows: temperature (T), 98.4°F; pulse (P), 96 beats/min and regular; respiratory rate (RR), 22 breaths/min; and blood pressure (BP), 92/68 mm Hg. Chest radiograph showed hyperinflation but no infiltrates or other abnormalities. Electrocardiogram revealed sinus tachycardia. Arterial blood gas (ABG) determination on room air indicated the following: pH, 7.44; arterial carbon dioxide pressure (PaCO_2), 38 mm Hg; arterial oxygen pressure (PaO_2), 54 mm Hg; base excess (BE), 2.2; bicarbonate (HCO_3^-), 25.9 mEq/L; and arterial oxygen saturation (SaO_2), 89.4%. Hemoglobin was 13.3 g/dL, and the white blood cell (WBC) count was $8.8 \times 10^3/\text{mm}^3$. Administration of MDI albuterol by reservoir showed little improvement in her peak flow rates.

Assessment: Pulmonary exacerbation.

Plan: Admitted to the hospital. Administer 2.5 mg albuterol and 0.5 mg ipratropium bromide via SVN; place on oxygen at 3 L/min by nasal cannula. Administer 40 mg of IV methylprednisolone and a brand of phenylephrine for nasal decongestion and sinus clearance.

Chapter 12

Self-Assessment Questions

1. Identify four nonsteroidal antiasthma drugs used in the management of chronic asthma; give generic and brand names.
Answer: Cromolyn sodium, montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo).

2. Which immunoglobulin is implicated in allergy and is termed *cytophilic*?

Answer: Immunoglobulin E (IgE).

3. Which type of asthma involves allergic reaction to an antigenic stimulus?

Answer: Extrinsic, or atopic.

4. Which type of helper T cell, Th1 or Th2, is involved primarily in the atopic allergic response?

Answer: Th2 cells (helper type 2 lymphocytes).

5. A resident wishes to order nebulized cromolyn sodium for a young patient with asthma in the emergency room who is wheezing and in moderate distress. Would you agree?

Answer: No. Cromolyn sodium, as a mediator antagonist, is a prophylactic agent to *prevent* mast cell degranulation and mediator release; the drug has no bronchodilating properties.

6. Which of the following could be recommended as possible choices for the patient with asthma in question 5: inhaled albuterol, inhaled salmeterol, inhaled ipratropium bromide, theophylline (either orally or intravenously)?

Answer: All the agents listed could be used in an acute asthma episode except for salmeterol because its pharmacokinetics are not useful for an acute attack.

7. A patient with asthma has been taking 40 mg of oral prednisone for 1 week after an acute asthma attack and an emergency department visit. His physician now wants to switch him to inhaled cromolyn and discontinue the oral prednisone. What is the risk in doing this, and what would you recommend?

Answer: There is a risk of adrenal insufficiency caused by the steroid therapy and HPA axis suppression and by the fact that cromolyn is not a steroid. A tapered dose regimen of the oral prednisone while the cromolyn is started could be recommended.

8. How does the mechanism of action of zafirlukast and montelukast differ from that of zileuton?

Answer: Zafirlukast and montelukast act by competitive antagonism of leukotriene receptors (CysLT₁ receptors), whereas zileuton acts by inhibition of the 5-lipoxygenase enzyme.

9. What is the recommended dosage and route of administration for zafirlukast, montelukast, and zileuton?

Answer: Zafirlukast—20 mg twice daily, by the oral route; montelukast—10 mg once daily, orally; zileuton—600 mg four times daily, or two 600 mg extended release (Zyflo CR) twice daily, orally.

10. Which of the three antileukotriene agents in question 9 offers the most convenient dosing and the fewest drug interactions?

Answer: Montelukast (Singulair), with once-daily dosing, and no significant drug interactions, such as those that can occur with zileuton or zafirlukast.

11. When would you recommend using omalizumab?

Answer: In a patient with uncontrolled moderate to severe asthma, especially uncontrolled by corticosteroids.

12. A 17-year-old patient with asthma has been treated for symptoms for the last 12 months. His symptoms have not improved despite the use of the highest dosage of an inhaled corticosteroid agent and regular use of salmeterol; in addition, trials on montelukast, cromolyn sodium, and oral theophylline have been unsuccessful. What would you recommend for this patient?

Answer: Omalizumab would be a great recommendation. The use of omalizumab may be able to decrease the use of corticosteroids being administered.

Clinical Scenario

Subjective: A 45-year-old white female is seen in the ED with a complaint of chest tightness, shortness of breath, and wheezing for the past 1.5 days. She also complains of a cough, with only occasional thin whitish sputum during that period. She denies any fever or chills. She was diagnosed with adult-onset asthma 3 years ago and is aspirin sensitive. She has no history of tobacco use. She has been using OTC racemic epinephrine as needed and, since about 4 months ago, has been taking oral theophylline 300 mg twice daily. She is alert but mildly anxious. On questioning, she states that she has been using OTC racemic epinephrine almost every 2 hours over the past 24 hours with little improvement. She states that she has been experiencing many headaches, upset stomach, some lack of appetite, and insomnia often during the week. It has been 2 to 3 hours since she last had an OTC racemic epinephrine treatment.

Objective: The patient's vital signs are as follows: temperature (T), 97°F; pulse (P), 112 beats/min and regular; blood pressure (BP), 135/90 mm Hg; and respiratory rate (RR), 22 breaths/min with no laboring. Expiration is slightly prolonged, but there is no use of accessory muscles. No cyanosis is evident. Auscultation reveals diffuse wheezes, greater on expiration than inspiration, and rhonchi bilaterally. Routine blood work later showed the following: hemoglobin, 13.5 g/dL; and white blood cell (WBC) count, $6.1 \times 10^3/\text{mm}^3$ with 13% eosinophils. Electrolytes were also found to be within normal limits except for a plasma glucose level of 281 mg/dL. A chest radiograph showed some hyperinflation bilaterally, with no infiltrates, no pneumothorax, and normal heart size. An arterial blood gas (ABG) measurement on room air revealed the following: pH, 7.38; arterial carbon dioxide pressure (PaCO₂), 42 mm Hg; arterial oxygen pressure (PaO₂), 72 mm Hg; base excess, + 0.3 mEq/L; and arterial oxygen saturation (SaO₂), 96%.

Assessment: Asthma exacerbation; increased heart rate and blood pressure secondary to asthma and use of racemic epinephrine.

Plan: Place patient on oxygen at 2 L/min by nasal cannula because of her hypoxemia (PaO₂, 72 mm Hg) and give 4 actuations of albuterol using an MDI with a holding chamber every 20 minutes. Complete a plasma theophylline level blood draw to confirm theophylline level. If she is better after therapy dismiss to home on oral prednisone, tapered dose for 1 week. Consider removing theophylline because of her headaches and replacing with low-dose inhaled corticosteroid; however, given her recent cough symptoms and aspirin sensitivity, she may be a good candidate for use of an antileukotriene agent. Continue a short-acting β agonist as needed, and monitor daily with a peak flow meter. Insist that she not use OTC racemic epinephrine.

Chapter 13

Self-Assessment Questions

1. Identify the disease states for which each of these drugs is used when inhaled as an aerosol: pentamidine, ribavirin, tobramycin, aztreonam, and zanamivir.

Answer: Pentamidine—*Pneumocystis jiroveci* pneumonia (PJP) prophylaxis in acquired immunodeficiency syndrome (AIDS) (last option); Ribavirin—respiratory syncytial virus (RSV) treatment with risk of severe or complicated infection; Tobramycin—management of *Pseudomonas aeruginosa* in CF; Aztreonam—management

of *Pseudomonas aeruginosa* in CF; Zanamivir—treatment of acute influenza infection.

2. Briefly explain the rationale for aerosolizing an antibiotic, such as tobramycin or aztreonam, in CF.

Answer: The oral route gives inadequate lung levels; inhaled and IV routes give higher lung tissue levels.

3. What is the brand name of aerosolized pentamidine?

Answer: NebuPent.

4. What is the dose and frequency for aerosolized pentamidine?

Answer: 300 mg four times a week (q4wk).

5. What device is approved for aerosolization of pentamidine?

Answer: Respirgard II.

6. Identify the common airway effects with aerosolized pentamidine and suggest a method for preventing or lessening these effects.

Answer: Cough, bronchoconstriction; pretreat with a β agonist.

7. What is a major risk to the caregiver when aerosolizing pentamidine to a patient with AIDS?

Answer: Contraction of tuberculosis (TB) infection.

8. What is the current CDC-recommended prophylactic treatment for PCP in patients with AIDS?

Answer: Use trimethoprim-sulfamethoxazole (TMP-SMX) orally as long as side effects are tolerated and acceptable. The use of inhaled pentamidine is an option.

9. What is the brand name and dose for aerosol ribavirin?

Answer: Virazole 6 g/300 mL (2%), 12 to 18 hr/day for 3 to 7 days.

10. What is the mechanism of action of ribavirin?

Answer: Virostatic; as a nucleoside analog, ribavirin interferes with viral transcription and replication.

11. Name two serious hazards when ribavirin is given to a patient undergoing mechanical ventilation.

Answer: (1) Occlusion of endotracheal tube; (2) expiratory valve and sensor occlusion.

12. In general, how can you prevent environmental contamination when delivering ribavirin to an oxygen hood?

Answer: By using a containment/scavenging system around the hood.

13. What is the recommended dosage for inhaled tobramycin?

Answer: Aerosolize 300 mg twice daily, alternating between 28 days on and 28 days off.

14. Identify common side effects that have been observed with aerosolized tobramycin.

Answer: Tinnitus and voice changes.

15. Name two potential hazards to family members with aerosolized tobramycin at home.

Answer: Exposure to aerosolized drug in ambient air may lead to (1) allergic reactions in those sensitive to the drug and (2) fetal harm in a pregnant female.

16. What is the recommended dosage for inhaled aztreonam?

Answer: 75 mg by Altera Nebulizer System three times daily (tid), alternating between 28 days on and 28 days off.

17. What should be done before a patient is prescribed inhaled aztreonam?

Answer: Collect baseline pulmonary function results to monitor FEV₁ and pretreat with a bronchodilator.

18. Give the brand name and dosage for zanamivir.

Answer: Relenza; 2 inhalations (10 mg) twice daily 12 hours apart, for 5 days.

19. In one sentence, describe the mechanism of action of zanamivir.

Answer: Zanamivir inhibits the viral enzyme neuraminidase, causing viral aggregation and clumping, thus preventing viral release and spreading.

20. Identify common hazards in the use of inhaled zanamivir.

Answer: Pulmonary function deterioration, including bronchospasm in those with reactive airway disease, and inappropriate treatment or undertreatment of nonviral bacterial infections.

21. What factors cause debate over the use of zanamivir in treating influenza?

Answer: Essentially cost versus efficacy—small reduction in symptoms; no inexpensive, easily available test to confirm influenza infection; and increased possible risk in airway disease.

Clinical Scenario

Subjective: Brody Hendrix is a 29-year-old adult male with CF. He has been admitted to the hospital with complaints of increasing cough, shortness of breath, and sputum production. He reports that his sputum is greenish. His recent history reveals that his last admission for exacerbation of cystic fibrosis was approximately 6 months ago. He has used albuterol by MDI, with 2 puffs qid, and recently began to use salmeterol, 2 puffs bid. He maintains himself on a regular regimen of CF medications, including iron and vitamin supplements and pancrelipase (Pancrease). Approximately 3 weeks ago, he complained of increasing pulmonary secretions and noted a mild elevation of his temperature. At that time, his physician prescribed ciprofloxacin, 500 mg orally bid, and he completed a course of 14 days, ending 5 days ago.

Objective: He is alert, oriented, and in no acute distress at this time. His skin is warm and dry. His vital signs are as follows: blood pressure (BP), 106/66 mm Hg; pulse (P), 88 beats/min and regular; respiratory rate (RR), 20 breaths/min; and temperature (T), 98.9°F. His respiratory pattern is normal, and there is no use of accessory muscles. Auscultation reveals scattered rales and wheezes bilaterally, both anteriorly and posteriorly. His cough is nonproductive during the examination. Chest radiograph shows hyperexpanded lung fields with linear fibrotic changes bilaterally over the lung fields. Cardiac silhouette shows mild right atrial hypertrophy. No consolidation or pleural effusion is seen. Complete blood count (CBC) results are as follows: hemoglobin, 13.2 g/dL; hematocrit, 38.6%; and white blood cell (WBC) count, $13.5 \times 10^3/\text{mm}^3$. Remaining blood values are within normal limits. Pulse oximetry measures 89% saturation on room air. His pulmonary function, measured approximately 2 months ago, shows forced vital capacity (FVC), 67% of predicted; FEV₁, 40% of predicted; forced expiratory flow 25% to 75% (FEF₂₅₋₇₅), 17% of predicted; RV, 260% of predicted; and TLC, 115% of predicted.

Assessment: Mr. Hendrix has an acute exacerbation of CF.

Plan: Continue with his usual cystic fibrosis medications (vitamins, iron supplement, pancreas enzymes). *Oxygen* is indicated by his SpO₂ (oxygen saturation by pulse oximetry) value. *Antibiotic therapy* will be needed to reduce his bacterial burden, as indicated by his temperature and WBC count. Because he has completed a course of ciprofloxacin and symptoms are now recurring, there is the possibility of resistance to the ciprofloxacin. A different, or at the least an additional, antibiotic may be needed. Recommend administering aerosolized tobramycin or aztreonam. An aggressive program of bronchial hygiene is

usual to clear his secretions and would include *chest physiotherapy* with postural drainage and percussion as tolerated for mobilization of secretions; β_2 agonist by aerosol to maintain airway patency; possible administration of the anticholinergic bronchodilator *ipratropium* by either SVN or MDI; and, finally, adequate fluid intake and balanced nutrition.

Chapter 14

Self-Assessment Questions

1. What is the difference between bacteriostatic and bactericidal antimicrobial agents?

Answer: Bacteriostatic agents inhibit the growth of bacteria, whereas bactericidal agents kill bacteria.

2. Give an example of a class of antimicrobials that kill in a concentration-dependent manner *and* in a concentration-independent manner.

Answer: Concentration-dependent antimicrobials include aminoglycosides, fluoroquinolones, and daptomycin. Concentration-independent antimicrobials include β lactams, tetracyclines, glycopeptides, and macrolides.

3. Describe at least three parameters that may indicate antibiotic failure in a patient.

Answer: Continued fever spikes, elevated WBC count, repeated positive cultures, and nonresolution or worsening of symptoms (e.g., hypotension or mental status change) may indicate antibiotic failure.

4. Why is combination antibiotic therapy useful? (Be specific.)

Answer: Antimicrobial combinations can provide broad-spectrum activity as part of an empiric regimen. Certain infections are polymicrobial and so require a combination of antimicrobials to be therapeutically effective. Antimicrobial combinations can be used for their synergistic effect and to reduce the emergence of resistance.

5. Describe the mechanism of action of penicillin antibiotics. Name at least two additional antibiotic classes with similar mechanisms of action.

Answer: Penicillins bind to cell wall proteins to inhibit the cross-linkage of peptidoglycan, which reduces the structural integrity of the cell wall, resulting in lysis. Cephalosporins, carbapenems, and monobactams have a similar mechanism of action.

6. Which β -lactam antibiotic is least likely to cause an allergic reaction in a patient with a penicillin allergy?

Answer: Aztreonam.

7. Name three antimicrobial agents that would be useful in the treatment of community-acquired pneumonia (CAP).

Answer: Macrolide (azithromycin or clarithromycin), ketolide (telithromycin), fluoroquinolone (levofloxacin or moxifloxacin), β lactam (amoxicillin-clavulanate), or doxycycline.

8. What is the antimicrobial agent of choice for treatment of *Pneumocystis pneumonia* (PCP)?

Answer: Trimethoprim-sulfamethoxazole (TMP-SMX).

9. What agents are considered first-line therapy for treatment of pulmonary tuberculosis?

Answer: Isoniazid, rifampin (rifampin), rifabutin, or rifapentine), pyrazinamide, and ethambutol.

10. Which antimicrobial agents are useful for the treatment of nosocomial pneumonia caused by *Pseudomonas aeruginosa*?

Answer: Carbapenem (excluding ertapenem), cefepime, ceftazidime, or piperacillin/tazobactam plus an aminoglycoside (gentamicin, tobramycin, or amikacin) or fluoroquinolone (ciprofloxacin or levofloxacin).

Clinical Scenario

Subjective: This is a 64-year-old White male with a history of COPD and recurrent pneumonia. The patient complains of productive cough with green sputum, fever, and worsening shortness of air (SOA). He also has gastroesophageal reflux disease (GERD) and chronic alcohol abuse.

Objective: Physical examination revealed the following vital signs: temperature (T), 102.2°F; blood pressure (BP), 150/85 mm Hg; heart rate (HR), 105 beats/min; respiratory rate (RR), 29 breaths/min; and oxygen saturation by pulse oximetry (SpO_2), 90% on 2 L oxygen (O_2), 82% on room air. The patient is an elderly male in acute distress; tachycardic, with a regular rhythm; bilateral crackles, with decreased breath sounds over lower left lobe. His white blood cell (WBC) count is 18.4×10^3 cells/mm³. Sputum demonstrated many WBCs, few epithelial cells, many gram-positive cocci in clusters with culture pending. His chest x-ray (CXR) film revealed left lower lobe (LLL) infiltrate.

Assessment: Because of the patient's past medical history of multiple hospitalization with recurrent pneumonia (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and symptoms consistent with a diagnosis of health care-associated pneumonia (HCAP) including productive cough, fevers, and SOA. The signs of infection include his elevated temperature, elevated heart and respiratory rates, bilateral wheezing, elevated WBC count, many WBCs in his sputum gram stain, and LLL infiltrate on CXR. The Gram stain revealed gram-positive cocci in clusters, which is consistent with the most likely pathogen in this patient, methicillin-resistant *Staphylococcus aureus* (MRSA).

Plan: Antimicrobial therapy should be initiated immediately with either IV vancomycin or IV linezolid. Although daptomycin also has excellent activity against MRSA, it cannot be used for pneumonia because this agent is inactivated by lung surfactants. After appropriate response to IV therapy, the patient could be discharged on oral (PO) linezolid to finish his course of treatment. Before discharge, the patient needs to be counseled on the importance of smoking cessation and decreased alcohol consumption.

Chapter 15

Self-Assessment Questions

1. Identify the four classes of ingredients found in cold medications.

Answer: Adrenergic decongestants, antihistamines (H_1 blockers), expectorants, and antitussives. *Note:* An analgesic may be added.

2. For each of the following agents, identify the category (e.g., adrenergic, antitussive): codeine, chlorpheniramine, phenylephrine, dextromethorphan, and pseudoephedrine.

Answer: Codeine—antitussive; chlorpheniramine—antihistamine; phenylephrine—adrenergic; dextromethorphan—antitussive; pseudoephedrine—adrenergic.

- What is the intended purpose of α -adrenergic agents in cold medications?

Answer: Topical vasoconstriction to open the upper (nasal) airway.

- What is the intended effect of antihistamines (e.g., histamine [H_1] blockers) in cold medications?

Answer: To dry secretions (rhinitis) produced by histamine release and stimulation of H_1 receptors.

- Are antihistamines in cold remedies H_1 or H_2 blockers?

Answer: H_1 blockers. (H_2 blockers, e.g., ranitidine [Zantac], are antiulcer drugs.)

- After you have imbibed several beers at a friend's house after taking a dose of Benadryl, should you drive home? Why, or why not?

Answer: No. Antihistamines cause drowsiness and alcohol produces an additive effect on this—reflexes are decreased.

- Identify the most common expectorant in over-the-counter (OTC) cold remedies.

Answer: Guaifenesin (glyceryl guaiacolate).

- Briefly explain how guaifenesin stimulates mucus production.

Answer: Probably through stimulation of vagal receptors in the stomach.

- List some specific fluids you would recommend to someone with a cold.

Answer: Water, juices, or milk.

- Differentiate a "cold" from the "flu."

Answer: Cold—nonbacterial upper respiratory infection with mild malaise and runny, stuffy nose (more localized than the flu); flu—systemic viral infection with fever, chills, headache, muscle ache, and extreme fatigue.

Clinical Scenario

Subjective: A 24-year-old student, a previously healthy male, is within normal weight limits and performs mild but irregular physical activity. He complains of mild malaise, a runny stuffy nose, sneezing, and a slight sore throat. He denies headache or muscle ache, describes the malaise as a very mild fatigue, and states that he noticed a gradually increasing rhinitis over a period of hours, with sneezing beginning during the first 6 hours of these symptoms.

Objective: He has no fever.

Assessment: His symptoms indicate a cold rather than the flu.

Plan: Point out that there is no "cure" if this is a rhinovirus infection. He should treat his symptoms, however. An adrenergic *decongestant* may be helpful in opening his nasal passages and reducing some of the rhinitis. The use of a topical agent will give fewer systemic effects, such as a feeling of shakiness, and central nervous system stimulation than an oral agent. Caution him to use the decongestant sparingly to avoid rebound nasal congestion; treating the rebound congestion with additional sprays can produce a self-sustaining congestion. An antitussive agent, such as dextromethorphan, can be helpful if he has a nonproductive, dry, irritating cough, particularly if this prevents adequate rest at night. The use of an antihistamine should be avoided, if possible, to prevent impaction of secretions and subsequent sinus problems. However, if an antihistamine is used, it should be taken only at night or when alert activity (including driving) is not needed. Rest and good nutrition, including fluid intake, will assist his own immune response to recover from the infection.

Chapter 16

Self-Assessment Questions

- For which disease state is an α_1 -proteinase inhibitor (API) indicated?

Answer: Congenital α_1 -antitrypsin (α_1 -AT) deficiency.

- What is the route of administration for an API?

Answer: Intravenous.

- What is the mode of action of APIs in treating emphysema associated with inadequate API levels?

Answer: IV administration of exogenous API increases blood levels and diffuses into the lung tissue to increase epithelial fluid levels, where the API inactivates the enzyme neutrophil elastase (NE), which can destroy lung tissue.

- Is treatment with an API indicated for age-related emphysema or in general for individuals who smoke and have emphysema later in life?

Answer: No. Use of API is recommended only for those who have congenital α_1 -AT deficiency and severe COPD. Such individuals often are smokers, which is a risk factor for development of COPD in α_1 -AT deficiency, usually at an early age (third or fourth decade).

- Identify three pharmaceutical formulations of nicotine that are used as smoking cessation aids.

Answer: The transdermal patch, chewing gum, lozenge, nasal spray, and inhaler.

- What is the usual effect of nicotine, whether in a smoking cessation aid or in cigarettes, on blood pressure?

Answer: Nicotine acts at the ganglionic synapses to increase blood pressure, with peripheral vasoconstriction; epinephrine is released from the adrenal medulla, contributing to hypertension, tachycardia, and vasoconstriction.

- Name two nonnicotine agents used in the treatment of smoking cessation.

Answer: Varenicline (CHANTIX) and bupropion (Zyban, Wellbutrin).

- What is the effect of inhaled nitric oxide (NO)?

Answer: Relaxation of the pulmonary vascular endothelium and reduction of pulmonary hypertension.

- Identify two potentially toxic byproducts of inhaled NO.

Answer: Methemoglobin and nitrogen dioxide.

- What is the usual dose of inhaled NO?

Answer: The recommended dose is 20 ppm, maintained up to 14 days or until the underlying oxygen desaturation has resolved and weaning from inhaled nitric oxide can be accomplished.

- Identify two disease states in which NO has been used to reverse pulmonary hypertension.

Answer: Persistent pulmonary hypertension of the newborn and acute respiratory distress syndrome.

- What is the greatest hazard in terms of pulmonary health with the delivery of Ventavis?

Answer: Ventavis is known to cause bronchospasm.

- What is the initial dose of Tyvaso?

Answer: Three breaths per treatment session (18 mcg), four times daily during waking hours.

- What letter in the COPD evidence-based strategy should roflumilast be utilized?

Answer: D

15. What are the four CTFR agents approved for use in the US?
Answer: Ivacaftor (Kalydeco)
 Lumacaftor/ivacaftor (Orkambi)
 Tezacaftor/ivacaftor (Symdeko)
 Elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets;
 co-packaged (Trikafta)
16. What is the trade name of the only inhaled insulin on the market?
Answer: Afrezza
17. What patient population should avoid the use of inhaled insulin?
Answer: Pulmonary patients, especially those with asthma and COPD.

Clinical Scenario

Subjective: The patient complains of shortness of breath on exertion and increasing fatigue during her usual activities. She reported that she had an uncle who had died “many years previously” in his middle age as a result of lung disease. She admitted that she had been a heavy smoker (around a pack per day) for 5 or 6 years but quit more than 8 years ago. She described having several attacks of “bronchitis” in the past year. She also described a small, but increasing, production of sputum during the past year, usually clear unless she had an episode of bronchitis.

Objective: Auscultation of her chest reveals expiratory wheezing, diminished breath sounds bilaterally, and a somewhat prolonged expiratory phase. There is no digital clubbing, cyanosis, pedal edema, or jugular distention. Vital signs are as follows: temperature (T), 98.8°F; blood pressure (BP), 110/76 mm Hg; pulse (P), 76 beats/min; and respiratory rate (RR), 24 breaths/min and regular. On room air, her reading on pulse oximetry is 91%. There is a mild elevation of her white blood cell (WBC) count ($13.1 \times 10^3/\text{mm}^3$), normal hemoglobin and hematocrit, normal electrolytes, and *Pseudomonas* and normal flora was found in her sputum. A chest radiograph showed some hyperlucency; hyperinflation with moderately lowered, somewhat flattened hemidiaphragms on full inspiration; and an infiltrate in the right lower lobe. Arterial blood gas (ABG) values on room air were as follows: pH, 7.35; partial pressure of arterial carbon dioxide (PaCO_2), 54 mm Hg; partial pressure of arterial oxygen (PaO_2), 66 mm Hg; bicarbonate (HCO_3^-), 30 mEq/L; and saturation of arterial oxygen (SaO_2), 92%. Pulmonary function tests revealed forced expiratory volume in 1 second (FEV_1) that was 60% of predicted, with an elevated residual volume (RV) and RV/total lung capacity (RV/TLC) ratio, an increased TLC above predicted, and a decreased diffusing capacity of the lung for CO (DL_{CO}).

Assessment: Her clinical and laboratory findings support a diagnosis of COPD. However, her smoking history is not sufficient to produce the degree of severity seen, and her age is incompatible with the usual presentation of COPD.

Plan: Obtain an API blood level because of suspicion of congenital α_1 -AT deficiency.

Chapter 17

Self-Assessment Questions

1. Can an aerosol formulation for oral inhalation be legally administered to neonates, infants, and pediatric patients?

Answer: Yes, using appropriate devices and techniques and with a duly licensed physician's order.

2. Can an adrenergic bronchodilator, such as albuterol, reduce airway resistance when used in neonates?

Answer: Yes. Multiple studies have found improved airway mechanics with aerosolized albuterol delivered by either MDI/reservoir system or nebulizer.

3. According to the data reviewed in this chapter, does the adult dose of an aerosol drug need to be reduced for neonatal and pediatric patients based on weight?

Answer: No. Because of multiple factors in neonatal and pediatric patients, the actual dose of an inhaled aerosol reaching the lungs is proportionately less than an adult lung dose and increases/decreases with increasing/decreasing age.

4. What aerosol delivery devices could be used with a 2-year-old child?

Answer: A nebulizer (with mask if necessary) or an MDI with a reservoir and mask.

Clinical Scenario

Subjective: A 24-month-old boy who was born at 27 weeks' gestation is brought to the ED in respiratory distress. His medical history is significant for bronchopulmonary dysplasia.

Objective: Vital signs are as follows: temperature, 99.5°F; pulse, 175 beats/min; respiratory rate (RR), 76 breaths/min; blood pressure (BP), 85/55 mm Hg; saturation of peripheral oxygen (SpO_2), 85% on room air. The physical examination reveals the presence of intercostal retractions, increased anteroposterior diameter, nasal flaring, and bilateral diffuse expiratory wheezing.

Assessment: The patient receives 1.25 mg unit dose via SVN. While receiving the aerosol, the patient's pulse rate climbs to 220 beats/min and he becomes cyanotic despite the use of oxygen to nebulize the drug. The patient is promptly intubated and mechanically ventilated.

Plan: Although the patient receives albuterol throughout his stay, one may recommend levalbuterol. Although the case did not detail the dose of albuterol given during the child's stay, it would be safe to say that it was a lower dose. The patient was prescribed albuterol syrup at discharge; however, other choices may include MDI formulations of albuterol or levalbuterol with a spacer device with attached mask or SVN formulation with mask.

Chapter 18

Self-Assessment Questions

1. List four general uses of skeletal muscle relaxants.

Answer:

- To facilitate endotracheal intubation.
- For muscle relaxation during surgery, particularly of the thorax and abdomen.
- To enhance patient-ventilator synchrony.
- To reduce intracranial pressure in intubated patients with uncontrolled intracranial pressure.
- To reduce oxygen consumption.
- To terminate convulsive *status epilepticus* and *tetanus* in patient's refractory to other therapies.
- To facilitate procedures or diagnostic studies.
- For selected patients who must remain immobile (e.g., trauma patients).

2. What are the two classifications of neuromuscular blocking agents?
Answer: Nondepolarizing and depolarizing.
3. Identify each of the following agents by classification type: vecuronium, succinylcholine, and pancuronium.
Answer: Vecuronium—nondepolarizing; succinylcholine—depolarizing; pancuronium—nondepolarizing.
4. Which type of neuromuscular blocker can be reversed?
Answer: Nondepolarizing.
5. What type of drug would you use to reverse vecuronium?
Answer: Cholinesterase inhibitor (e.g., neostigmine).
6. Identify another drug that you would want to give before you reverse vecuronium.
Answer: Atropine or glycopyrrolate (i.e., antimuscarinic agents).
7. Briefly explain why you might need to paralyze a patient receiving mechanical ventilation.
Answer: To relax the chest wall and prevent spontaneous breathing efforts that are out of phase with the ventilator, causing increased intrathoracic pressure and decreased alveolar ventilation.
8. Neuromuscular blocking agents do not block consciousness; what two types or classes of drugs would be indicated in a paralyzed patient on mechanical ventilation?
Answer: Analgesics and sedatives.
9. Identify at least two neuromuscular blocking agents that would be preferred for paralysis in a patient receiving mechanical ventilation (assume normal renal and hepatic function).
Answer: Vecuronium has minimal histamine release and cardiovascular effects; atracurium and rocuronium are also alternatives.
10. You are called to the recovery room to set up a ventilator for an older patient who has just undergone a total hip replacement and has stopped breathing after a single dose of succinylcholine. What might the problem be?
Answer: Atypical plasma cholinesterase.
11. What would you do first to assess a ventilated patient who is restless and “fighting” the ventilator before using a paralyzing agent?
Answer: Assess ventilator function and patient status: (1) ventilator—possible malfunction; inappropriate settings (flow, FiO_2 , volume, inspiratory/expiratory [I:E] ratio); (2) patient—airway patency, SaO_2 or SpO_2 , possible pain or anxiety requiring analgesia and sedation rather than paralysis.

Clinical Scenario

Subjective: A 64-year-old White female presents with a complaint of shortness of breath and congestion along with fatigue and lethargy over the last 3 days. She has a history of diabetes mellitus, hypertension, and COPD secondary to smoking. She has had a productive cough of yellow-greenish sputum and states she has had fever and chills over the past several days.

Objective: Pulse (P), 130 beats/min; blood pressure (BP), 100/72 mm Hg; temperature (T), 101.3°F; and respiratory rate (RR), 30 breaths/min, with a moderate amount of respiratory distress. On auscultation, breath sounds are diminished bilaterally. An electrocardiogram shows sinus tachycardia. Chest radiograph shows bilateral interstitial infiltrates. Her

white blood cell (WBC) count is $23.7 \times 10^3/\text{mm}^3$ with 35% bands, hemoglobin is 11.2 g/dL, hematocrit is 33.2%, and electrolytes are within normal limits, except for glucose, which is 250 mg/dL. Arterial blood gas (ABG) values on a 100% nonrebreather mask are as follows: pH, 7.2; arterial carbon dioxide pressure (PaCO_2), 50 mm Hg; arterial oxygen pressure (PaO_2), 55 mm Hg; and arterial oxygen saturation (SaO_2), 82%.

Assessment: The patient is not effectively oxygenating. As a result, the patient has a $\text{PaO}_2/\text{FiO}_2$ ratio of 55. The patient is very tachypneic and has impending ventilatory failure.

Plan: Intubate and ventilate.

Chapter 19

Self-Assessment Questions

1. What is a diuretic?
Answer: A diuretic is any substance that increases urine output.
2. Identify the five major groups of diuretics used clinically.
Answer: Osmotic, carbonic anhydrase inhibitors, thiazide, loop, and potassium sparing.
3. If an agent, such as one of the loop diuretics, causes loss of K^+ , how would this lead to metabolic alkalosis?
Answer: Sodium that is still reabsorbed will exchange for either potassium or hydrogen. Low potassium, resulting from excretion, forces reabsorbed sodium to exchange for hydrogen, depleting hydrogen ions and raising pH. Hydrogen is also excreted as a result of the diuretic, adding to the alkalosis. Potassium replacement is usually necessary to prevent hypokalemia.
4. Which diuretics would preserve K^+ ?
Answer: The potassium-sparing agents, such as amiloride, triamterene, or spironolactone.
5. What is the potential effect of a carbonic anhydrase inhibitor on acid–base balance?
Answer: A loss of bicarbonate, leading to metabolic acidosis.
6. Explain how a diuretic, such as furosemide, can be helpful in acute CHF with pulmonary and vascular edema.
Answer: A potent diuretic such as furosemide will cause excretion of volume from the circulatory system by limiting sodium and therefore water retention. This will decrease the amount of volume leaking from the vasculature both in the lung and in the periphery, as well as venous return to the heart. Reduced pulmonary edema will improve oxygenation, which will also improve oxygen available to the heart. Reduced preload also reduces the work of the myocardium. Reduced preload and improved oxygenation are beneficial to restoring heart function.
7. Which diuretic agent has a vasodilatory effect when used for long-term treatment?
Answer: Hydrochlorothiazide (HCTZ).
8. In an otherwise healthy adult with mild hypertension, what diuretic agent should be considered the first-line treatment?
Answer: HCTZ.
9. Which diuretic agent has been successfully used in the management of ARDS?
Answer: Furosemide.
10. Match each of the following sets of drugs on the left with the most likely interaction on the right.

Answer:

Gentamicin <i>PLUS</i> furosemide	Hyperglycemia
Hydrochlorothiazide <i>PLUS</i> prednisone	Ototoxicity and nephrotoxicity
Spironolactone <i>PLUS</i> enalapril	Hyperkalemia
Hydrochlorothiazide <i>PLUS</i> carbamazepine	Hyponatremia

Clinical Scenario

Subjective: A 73-year-old White male presents to the emergency department with a chief complaint of severe dyspnea that began about 8 hours before presentation. The patient's history is significant for long-standing hypertension and coronary artery disease. He states that he began feeling dyspneic the night before presentation and then awoke at about 5:00 AM severely dyspneic and coughing up white, foamy phlegm. When queried about his compliance with his medicines, he admits that he sometimes forgets to take his clonidine. The patient has chronic renal insufficiency and has had right inguinal hernia repair. He denies any allergies. The patient is taking the following medications: clonidine 0.1 mg PO bid; atenolol 50 mg PO hs (at bedtime) each night; aspirin 325 mg PO qd; transdermal nitroglycerin 0.4 mg/h (he places a patch on in the morning and takes it off at bedtime); and furosemide 40 mg PO q AM.

Objective: Physical examination reveals an elderly white male in obvious respiratory distress. His vital signs are as follows: pulse (P), 120 beats/min and regular; respiratory rate (RR), 32 beats/min; blood pressure (BP), 230/140 mm Hg, and he is afebrile. His neck shows positive jugular venous distension. Heart auscultation reveals a regular rate, with a systolic ejection murmur (I/VI), negative S_3 , and positive S_4 . His lungs demonstrate bibasilar inspiratory crackles half of the way up the thorax. His abdomen is flat, and bowel sounds are present; no masses or tenderness are identified. His extremities are slightly cool, and pulses are felt in all extremities but are somewhat thready.

The patient's laboratory results are as follows: sodium (Na), 138 mEq/L; potassium (K), 3.6 mEq/L; blood urea nitrogen (BUN), 40 mg/dL; and creatinine, 2.8 mg/dL. His electrocardiogram shows sinus tachycardia with inferior Q waves and lateral Q waves of questionable significance. A chest radiograph shows mild cardiomegaly with bilateral infiltrates consistent with pulmonary edema.

Assessment: This is a 73-year-old White male with ischemic heart disease, hypertension, and chronic renal insufficiency. His history, physical examination, and diagnostic data are consistent with acute pulmonary edema. His blood pressure is markedly elevated. There is a history of possible medical noncompliance, which would make one suspicious that he has not taken his clonidine. Acute hypertension in the face of already impaired left ventricular systolic function is a common cause of acute pulmonary edema. Of note, the patient does have some evidence of renal insufficiency with an elevated creatinine level. His potassium is at the lower end of normal, probably secondary to his furosemide.

Plan: This patient is currently taking furosemide 40 mg daily; thus an acceptable approach would be to double the oral dose and give it intravenously. Therefore, furosemide 80 mg intravenously would be a reasonable choice. If within 30 to 45 minutes of receiving IV furosemide the patient has not begun to increase

urine output, another loop diuretic would be reasonable. However, typically the preceding dose of furosemide would be doubled (to 160 mg in this case) and administered. The patient does have mild renal insufficiency and is taking a β blocker. Both of these probably attenuate the normal potassium wasting seen with diuretics; however, with vigorous diuresis, he would most certainly become hypokalemic without potassium replacement. This can lead to dangerous arrhythmias, particularly in patients with ischemic cardiomyopathy. The potassium should be monitored closely and administered to a level of 4.0 mEq/L or greater.

Chapter 20

Self-Assessment Questions

1. What is the difference between sedation and analgesia?
Answer: Sedation—decreased response to stimuli; relaxation; analgesia—relief of pain.

2. Identify the general class (sedative-hypnotic, analgesic, tranquilizer, anesthetic, antipsychotic) of each of the following agents: lorazepam, phenobarbital, doxapram, chloral hydrate, thiopental, midazolam, nitrous oxide, chlorpromazine, halothane, morphine, and ibuprofen.

Answer: Lorazepam—minor tranquilizer (antianxiety); phenobarbital—sedative-hypnotic; doxapram—respiratory stimulant; chloral hydrate—nonbarbiturate sedative-hypnotic; thiopental—general (IV) anesthetic; midazolam—general anesthetic; nitrous oxide—general anesthetic (gas); chlorpromazine—antipsychotic; halothane—general anesthetic (liquid-gas); morphine—narcotic analgesic; ibuprofen—nonsteroidal antiinflammatory drug (NSAID) and analgesic.

3. You are planning to extubate and remove a patient from the ventilator. However, the nurse administers a large dose of lorazepam (Ativan) for anxiety. What problem may occur if you proceed?

Answer: Hypoventilation, depressed ventilatory drive.

4. What is the most serious side effect of tranquilizers, sedatives, or analgesics (especially opioids)?

Answer: Central nervous system depression resulting in respiratory depression—hypoventilation or respiratory arrest.

5. You have two patients, both of whom have overdosed on central nervous system depressants: *Patient 1 is comatose, cyanotic, with dilated pupils. Patient 2 is comatose, cyanotic, with pinpoint pupils.* Which patient may have taken a barbiturate and which may have taken a narcotic analgesic?

Answer: Barbiturate—Patient 1; narcotic—Patient 2.

6. Identify your initial priorities as a respiratory therapist in caring for a patient with an overdose of tranquilizers.

Answer: (1) Maintenance or establishment of airway; (2) provide ventilation; and (3) supplemental O_2 , as needed, to maintain PaO_2 .

7. What is the mode of action of the benzodiazepines?

Answer: Benzodiazepines bind to benzodiazepine receptors in the central nervous system and facilitate the action of γ -aminobutyric acid (GABA) in inhibiting neuronal transmission through increased chloride ion flow.

8. Identify an agent that can reverse the effects of benzodiazepines, such as midazolam and triazolam.

Answer: Flumazenil.

9. Would barbiturates be helpful in managing pain in a ventilated patient?

Answer: No, unless a dose capable of producing unconsciousness is used. There is no direct effect on pain transmission.

10. Would meperidine be helpful in preventing or lessening the perception of pain?

Answer: Yes; meperidine (Demerol) is a morphine-like narcotic and will occupy opiate receptors to block nerve transmission of pain.

11. Suggest an analgesic for minor pain for a patient with a bleeding disorder, such as hemophilia, or a patient who is taking an anticoagulant, such as warfarin.

Answer: Acetaminophen would be the drug of choice. Aspirin and NSAIDs can both inhibit platelet aggregation and prolong bleeding times, even in normal subjects, and should be avoided in those with bleeding disorders.

12. Are there any serious side effects to the use of a ventilatory stimulant, such as doxapram?

Answer: Yes; central nervous system stimulation to the point of seizures.

Clinical Scenario

Subjective: A 35-year-old Black male was admitted to the hospital with lethargy after being found in his apartment by a friend. An empty bottle of amitriptyline pills was lying next to the man. In the emergency room (ER), the patient became more lethargic to the point of unresponsiveness and developed hypopnea and bradypnea. He was intubated and mechanically ventilated with a volume-cycled ventilator. The patient had a history of depression but had been in good physical health. He was taking amitriptyline, which was prescribed by his psychiatrist for his depression. He has no allergies, and his past medical history and family history were unremarkable.

Objective: Physical examination revealed a mesomorphic male appearing to be his stated age. His vital signs were as follows: temperature (T), 102.2°F rectally; pulse (P), 140 beats/min; respiratory rate (RR), 12 breaths/min on an assist/control (A/C) rate of 12 breaths/min; blood pressure (BP), 110/60 mm Hg, right arm, supine. Head, eyes, ears, nose, and throat (HEENT) were unremarkable except for oral endotracheal tube (ETT) in place. His chest was normoresonant to percussion and his lungs had clear breath sounds bilaterally. Cardiovascular examination revealed that on palpation, the point of maximal impulse was located normally in the fifth intercostal space in the midclavicular line. Auscultation revealed normal S₁ and S₂ without murmurs, gallops, or rubs. He had normal jugular venous pressure, and his pulses were 2+ throughout. The man's abdomen was mildly distended with absent bowel sounds. No masses or organomegaly were present. His extremities were unremarkable, and his skin was very warm and dry. He was unresponsive to visual, auditory, or tactile stimuli, and his pupils were equally dilated and sluggishly responsive to light. All of his extremities were flaccid, and his reflexes were 1+ throughout. His plantar reflexes were downgoing. Laboratory results revealed normal hemogram, electrolytes, blood urea nitrogen (BUN), creatinine, and liver function test results. The tricyclic antidepressant (TCA) level was in the toxic range. His chest radiograph was normal. The ETT was approximately 2 cm above the carina. The electrocardiogram showed sinus tachycardia at 140 beats/min with prolonged PR and QRS intervals. Arterial blood gas (ABG) on A/C ventilation at 12 breaths/min, with a tidal volume (V_T) of 800 mL and a fraction of inspired oxygen (FiO₂) of 1, resulted in the following:

pH, 7.44; arterial carbon dioxide pressure (PaCO₂), 38 torr; arterial oxygen pressure (PaO₂), 550 torr.

Assessment: The patient has had a TCA overdose, confirmed by subjective data submitted by his friend finding an empty bottle of amitriptyline pills and objective data found from the toxicology screen showing high levels of tricyclic antidepressant (TCA) in his blood. The patient is being mechanically ventilated because of depression of his respiratory drive from the TCA.

Plan: Treat with activated charcoal via nasogastric tube, properly hydrate with IV fluids, and monitor. Wean FiO₂, as PaO₂ is within normal range at 100% O₂. Extubate after respiratory status has been restored. Get a psychiatric evaluation after extubation.

Chapter 21

Self-Assessment Questions

1. In which phase of the cardiac cycle does ventricular contraction occur?

Answer: Systolic phase.

2. Identify three functions that regulate MAP.

Answer: Heart rate, stroke volume, and systemic ventricular resistance

3. Which measurements, taken by a pulmonary artery catheter, are estimates of intravascular volume?

Answer: Central venous pressure and pulmonary capillary wedge pressure.

4. Hypotension is first managed by what mode of therapy?

Answer: Fluid administration.

5. What vasopressor acts only on the α receptors within the vasculature?

Answer: Phenylephrine.

6. Which agents exert an inotropic effect on the heart?

Answer: Dobutamine, isoproterenol, digoxin, and milrinone.

7. What electrolyte abnormality may potentiate the adverse effects of digoxin?

Answer: Hypokalemia.

8. What drug should be given for the management of extravasation caused by vasopressors?

Answer: Phentolamine.

9. What Vaughan Williams class of antiarrhythmics acts on the fast Na⁺ channels in the myocardium?

Answer: Class I (IA, IB, and IC).

10. What antiarrhythmic agent is structurally similar to amiodarone but has an improved side effect profile?

Answer: Dronedarone.

11. In patients taking dofetilide, at what Q-T_c interval should the drug be discontinued because the risk for torsades de pointes becomes too great?

Answer: Q-T_c interval > 500 msec.

12. Which antiarrhythmic agent is highly associated with the development of SLE?

Answer: Procainamide.

13. Identify the four categories of SCD.

Answer: Ventricular fibrillation (VF), pulseless ventricular tachycardia (PVT), pulseless electrical activity (PEA), and asystole.

14. What medication is indicated for treatment of asystole and pulseless electrical activity but not ventricular fibrillation or pulseless VT during cardiac arrest?

Answer: Atropine.

15. What are the two alternative routes of medication administration during cardiac arrest when an IV route is not available?

Answer: Intraosseous and endotracheal routes.

16. In a patient with septic shock, what is the pH in which the Surviving Sepsis Guidelines recommend utilizing NaHCO_3 therapy?

Answer: A pH less than 7.15.

17. When medications are administered via the endotracheal route during cardiac arrest, the dose should be increased by how many times the usual IV dose?

Answer: 2 to 2.5 times.

Clinical Scenario 1

Subjective: A 28-year-old female was rushed to the ED of a local hospital by paramedic staff after she collapsed suddenly at work. When she collapsed the staff in her office called for an ambulance, but basic life support had not been started. It was reported that she was in ventricular fibrillation when the paramedic staff arrived at the scene.

Objective: The paramedics promptly administered two shocks with a defibrillator, and after the second shock, a pulse could be felt. On arrival to the hospital, the patient's blood pressure dropped to 85/42 mm Hg and the cardiac monitor showed supraventricular tachycardia (SVT) of 170 beats/min.

Assessment: The patient is hypotensive and in SVT.

Plan: Fluids should be initiated before any vasopressors. Fluids are the mainstays for improving hypotensive episodes. Rapid administration of adenosine is implemented to terminate the SVT. Because of its ultrashort half-life adenosine is best administered through a central line for rapid arrival at the site of action or, if given through a brachial line, the arm should be held in the upright position, followed almost instantly by a saline flush.

Clinical Scenario 2

Subjective: A 49-year-old man is visiting his mother, who had been admitted to a nursing home for long-term rehabilitation because of a spinal cord injury. He goes to the bathroom, and a few minutes later, his mother hears a loud thud; she calls out to him, but there is no response. After an additional 3 minutes, the head nurse and the clinical pharmacist find him lying in the bathroom, initiate cardiopulmonary resuscitation (CPR), and obtain the code cart.

Objective: The initial electrocardiography (ECG) reading reveals pulseless electrical activity (PEA).

Assessment: PEA.

Plan: Administer both epinephrine and atropine at a dose of 1 mg rapid IV push followed by a 20-mL normal saline flush. Defibrillate the patient. Administer amiodarone 300 mg. After administration of the 300-mg IV bolus, all patients should be started on continuous infusion, delivering amiodarone at a rate of 1 mg/min for 6 hours and then decreasing to 0.5 mg/min for 18 hours, eventually converting to the oral formulation.

Chapter 22

Self-Assessment Questions

- What is the systolic and diastolic blood pressure goal for patients without any comorbidities?
Answer: Less than 150/90 mm Hg.
- List the adverse effects associated with angiotensin-converting enzyme inhibitors (ACEIs).
Answer: The most common ACEI-induced adverse effect is a persistent nonproductive dry cough, with an incidence of 20% to 30%. ACEI-induced adverse effects include rash, dysgeusia, hyperkalemia, orthostatic hypotension, blood dyscrasias, angioedema, and proteinuria.
- Which antihypertensive agents are preferred in the treatment of Black patients without any comorbidities?
Answer: Thiazide-type diuretics and calcium channel blockers.
- Which of the β blockers possess intrinsic sympathomimetic activity (ISA)?
Answer: The β blockers with ISA are acebutolol, carteolol, penbutolol, and pindolol.
- Which of the β blockers possess selective β_1 -blocker activity?
Answer: Acebutolol, atenolol, betaxolol, bisoprolol, and metoprolol.
- List adverse effects associated with α_1 -adrenergic antagonists.
Answer: α_1 -Adrenergic antagonist adverse effects include orthostatic hypotension, dizziness, syncope, reflex tachycardia, palpitations, and headaches. These adverse effects are generally a manifestation of the first-dose phenomenon.
- What are the most common side effects of nitrates?
Answer: The most common side effects of nitrates include tachycardia, palpitations, headaches, dizziness, and flushing.
- List metabolic effects associated with thiazide diuretics.
Answer: The metabolic effects of thiazide diuretics include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, and hyperglycemia.
- Name five medications that may cause drug-induced increases in blood pressure.
Answer: Five drugs that may cause drug-induced increases in blood pressure are venlafaxine, cyclosporine, ma huang, ibuprofen, and rofecoxib.
- Which calcium channel blocker is most likely to cause constipation?
Answer: Verapamil is the calcium channel blocker most likely to cause constipation.
- Identify the best available parameter to monitor the effects of warfarin.
Answer: The international normalized ratio is the best parameter available to monitor the effects of warfarin.
- What is the antidote for heparin?
Answer: Protamine is the antidote for heparin.
- What is the mechanism of action of warfarin?
Answer: Warfarin exerts its effect by interfering with the hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X.
- List the commercially available oral factor Xa inhibitors.
Answer: Apixaban and rivaroxaban.
- Identify the commercially available oral direct thrombin inhibitor.
Answer: Dabigatran.
- List the common CYP3A4 and P-glycoprotein inhibitors.
Answer: Amiodarone, clarithromycin, erythromycin, and ketoconazole.
- Name the pharmacologic class responsible for inhibiting the final pathway in platelet aggregation.
Answer: The glycoprotein IIb/IIIa inhibitors are responsible for inhibiting the final pathway in platelet aggregation.

18. Which thrombolytic is preferred for massive pulmonary embolism?
Answer: Streptokinase is the thrombolytic recommended for patients older than 75 years of age who present with ST segment elevation MI.
19. Name the only ACEI that is available in a parenteral dosage form.
Answer: Enalaprilat is the only ACEI that is available in a parenteral dosage form.
20. Identify the best available parameter to monitor the effects of heparin.
Answer: Activated partial thromboplastin time (APTT) is the best parameter available to monitor the effects of heparin.
21. Is clopidogrel or ticlopidine superior to aspirin for stroke prevention?
Answer: Clopidogrel has no demonstrated superiority to aspirin except for patients who have peripheral vascular disease. Both clopidogrel and aspirin are first-line therapies for stroke prevention. Ticlopidine has demonstrated superiority to aspirin; however, because of its deleterious side effect profile, ticlopidine is a second-line therapy for stroke prevention. Stroke prevention pharmacotherapy is lifelong.

Clinical Scenario

Subjective: A 75-year-old male presents to the ED complaining of chest pain of 1 hour in duration. He has had intermittent chest pain for the past week. He describes experiencing substernal pain that radiates down his left arm. The pain is associated with diaphoresis and is not relieved by change in body position. He has had a history of hypertension for the past 10 years. He has no history or family history for coronary artery disease.

Objective: The patient is currently taking labetalol, 200 mg twice daily, and an enteric-coated aspirin, 81 mg daily. He has no known allergies. On physical examination, he appears anxious and is complaining of chest pain. His vital signs are as follows: blood pressure (BP), 140/70 mm Hg; pulse (P), 74 beats/min; and respiratory rate (RR), 20 breaths/min. His heart sounds are normal, with no murmurs or gallops present. His lungs are clear on auscultation, and his abdomen, extremities, and fundoscopic examination are unremarkable. His skin is cool and clammy. Electrocardiography (ECG) displays evidence of sinus bradycardia with a heart rate of 49 beats/min. His cardiac enzymes all were elevated (creatinine kinase [CK], 200 U/L; CK-MB [CK isoenzymes found in muscle and brain fractions], 20 U/L; and troponin I, 2 mcg/mL).

Assessment: A non-ST segment elevation MI.

Plan: This patient does not have ST segment elevation MI and therefore is not a candidate for thrombolytic therapy. However, glycoprotein IIb/IIIa inhibitors would provide a benefit by inhibiting platelet aggregation and thrombus formation after an atherosclerotic plaque rupture. The use of glycoprotein IIb/IIIa inhibitors reduces the risk of death or nonfatal MI.

Chapter 23

Self-Assessment Questions

1. What is the *International Classification of Sleep Disorders, 3rd Edition*, and what information does it contain?
Answer: The ICSD-3 was published in 2014 by the American Academy of Sleep Medicine. Insomnia, sleep-related

breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and other sleep disorders are the seven main categories of sleep disorders covered by the ICSD-3.

The split of narcolepsy into types 1 and 2 and the addition of a treatment-emergent CSA diagnosis are the three most significant changes from ICSD-2. Chronic insomnia has also been combined into a single condition. In addition, many disorders now have updated diagnostic standards. Sleep medicine specialists and other healthcare professionals must become familiar with these changes.

2. What are the electroencephalographic correlates of wakefulness and sleep stages N1, N2, N3, and REM?
Answer: See electroencephalography (EEG) column in [Table 23.1](#):
N1, formerly known as Stage 1: Low-voltage, mixed-frequency waves (2 to 7 Hz range), mainly irregular theta activity, triangular vertex waves.
N2, formerly known as Stage 2: Relatively low-voltage, mixed-frequency waves, some low amplitude theta and delta activity.
N3, formerly known as Stages 3 and 4: $\geq 20\%$ to 50% of the epoch consists of delta (0.5 to 2 Hz) activity.
Stage REM: EEG is relatively low voltage with mixed frequency resembling N1 sleep.
3. What type of drug had been used for centuries to promote sleep onset and maintenance?
Answer: Opium.
4. What class or classes of drugs have replaced opium?
Answer: Barbiturates, then benzodiazepines, then nonbenzodiazepines.
5. How many people in the United States experience chronic sleep disorders?
Answer: Approximately 50 to 70 million adults in the United States suffer chronically from sleep disorders.
6. Who was von Economo, and what theories guided his neuroanatomic exploration of brain regions involved in the processes of initiating and maintaining wakefulness and sleep?
Answer: He was a physician who, in a series of postmortem examinations on the brains of patients who had succumbed to encephalitis lethargica, observed that lesions in the rostral midbrain and posterior hypothalamus had a profound effect on sleep and wakefulness.
7. What is the ascending activating system (AAS)?
Answer: A system of cell bodies that originate in the brainstem and innervate the midbrain and cortex.
8. How do neurons within the ventrolateral preoptic (VLPO) area affect sleep?
Answer: Onset of activity within the VLPO nuclei orchestrates the onset and maintenance of non-rapid eye movement (NREM) sleep.
9. What are the suprachiasmatic nuclei (SCN), and what are intrinsic discharge properties exhibited by many of its neurons?
Answer: SCN are the neuroanatomical sites of the primary mammalian biologic clock. Subpopulations of SCN neurons exhibit spontaneous patterns of discharge activity, and accordingly, are described as self-sustaining neural oscillators, or pacemakers.
10. Define chronobiology and chronopharmacology.

Answer: Chronobiology is the study of mechanisms contributing to the periodicity of biologic processes. Chronopharmacology is the study of time-dependent variations in pharmacology.

11. Describe pharmacologic treatments for insomnia.

Answer: See Table 23.3. Benzodiazepine (BZD) receptor agonists—estazolam, flurazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem, zolpidem CR; and selective melatonin receptor agonist—ramelteon.

12. What is the difference between restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)?

Answer: Restless legs syndrome is a chronic neurologic disorder characterized by unpleasant sensations in the legs and a compelling urge to move them while the patient is awake. Periodic limb movement disorder is defined as periodic episodes of spontaneous, repetitive, and highly stereotyped involuntary limb movements that occur during sleep.

13. What is the tetrad of clinical symptoms that defines narcolepsy?

Answer: Narcolepsy is characterized by a tetrad of clinical symptoms: (1) persistent excessive daytime sleepiness, (2) cataplexy, (3) hypnagogic hallucinations, and (4) sleep paralysis.

14. Give two examples of a parasomnia, and name the class of drugs routinely used in the treatment of these sleep disorders.

Answer: REM sleep behavior disorder and somnambulism. A common pharmaceutical treatment for both REM and NREM sleep parasomnias is a long-acting benzodiazepine.

15. What types of principal complaints characterize insomnia, and what drug classes are used to treat this disorder?

Answer: Insomnia is characterized by difficulty in falling asleep or staying asleep, insufficient sleep, multiple nocturnal awakenings, early morning awakening with inability to resume sleep, or nonrestorative sleep. Table 23.3 describes some of the primary drugs used to treat insomnia. See answer to question 11.

Clinical Scenario

Subjective: The patient was a 59-year-old White male with a body mass index (BMI) of 27 and a history of hypertension, arthritis, and depression. He presents to the sleep clinic with chief complaints of excessive daytime sleepiness, awakening from nocturnal sleep after 2 to 3 hours, and prickly sensations in the legs that coincide with nocturnal awakenings but are temporarily relieved by walking. He also reports experiencing the same prickly sensations in his legs during long trips in the car, regardless of the time of day. The sensations in his legs also spontaneously occur 2 to 3 evenings per week during the evening hours.

Objective: Analysis of polysomnography data revealed a sleep efficiency of 94% with a sleep latency of 5 minutes. The arousal index was 15 arousals per hour of sleep. Distribution of sleep stages was notable for an increased amount of N2 and REM sleep with a reduced amount of N3 sleep. The REM latency was normal. Periodic leg movements occurred 41 times per hour of sleep and resulted in 11 arousals per hour of sleep. There were no arrhythmias noted on the ECG. No snoring was noted with the patient in the lateral position. The apnea/hypopnea index (number of apneas and hypopneas per hour of sleep) was mildly elevated at 8.2 with a further increase to 13.6 events per hour during REM sleep. Oxyhemoglobin desaturation reached a nadir of 82% in REM sleep and 86% in NREM sleep.

Assessment: The patient suffers from periodic limb movement disorder and obstructive sleep apnea (OSA).

Plan: Treatment for the both RLS and nocturnal PLMD should be considered. Treatment is usually undertaken with a dopaminergic agent, benzodiazepine, or opiate and reduction of medications and behaviors known to provoke symptoms. Treatment for the patient's mild sleep apnea could include weight loss, upper airway surgery, dental devices, or continuous positive airway pressure (CPAP).

Appendix B

Units and Systems of Measurement

OUTLINE

Scientific Notation

Use of Scientific Notation

Abbreviations of Measures

Metric System

International System of Units (Système International D'Unités [SI Units])

SI Base Units

SI-Derived Units

Temperature Scales and Temperature Conversions

Conversion: Centigrade/Fahrenheit

Liquid Metric Conversions

Solid Metric Conversions

Household Units

Ratios and Percent Solutions

Calculation of Milliequivalents (mEq)

Drug Administration Times

Estimating Lean Body Weight

Lean Body Weight Calculation

Scientific Notation

Scientific notation is a method for expressing very large or very small numbers, using a single digit multiplied by a whole number power of 10.

Use of Scientific Notation

Place the decimal point of the number to the right of the first nonzero digit.

Multiply the number by 10 raised to a power equal to the number of places moved by the decimal point.

The exponent of 10 is positive for moves to the left and negative for moves to the right.

Example of a large number: 2292.0 is the same as 2.292×10^3 .

Example of a small number: 0.002292 is the same as 2.292×10^{-3} .

Abbreviations of Measures

cc or cu. cm	≡ cubic centimeters (1/1000 L)
cL	≡ centiliter (1/100 L)
dr	≡ dram or drachm
fl. oz	≡ fluid ounces
ft	≡ foot or feet
g	≡ gram

gal or gals	≡ gallons
gr	≡ grains
gtt	≡ drops
hr	≡ hour
IU	≡ international units (SI)
kg	≡ kilogram (1000 g)
L or l	≡ liter
lb or lbs	≡ pounds
m	≡ meter
m or min	≡ minims
mcg or µg	≡ microgram (1/1,000,000 g)
meq or mEq	≡ milliequivalent
mg	≡ milligram (1/1000 g)
min	≡ minutes
mL	≡ milliliter (1/1000 L)
mm	≡ millimeter 1/1000 m)
O, pt, or pts	≡ pints
oz or ozs	≡ ounces
sc	≡ scruple
sec	≡ seconds
st	≡ stones
T or tbsp	≡ tablespoon
t or tsp	≡ teaspoon
µL	≡ microliter (1/1,000,000 L)

Metric System

The metric system is based on multiples or fractions of 10.

Prefix	Scale
Kilo-	10^3
Hecto-	10^2
Deca-	10^1
Base Unit	$10^0 \equiv 1$
Deci-	10^{-1}
Centi-	10^{-2}
Milli-	10^{-3}
Micro-	10^{-6}
Nano	10^{-9}
Pico	10^{-12}

International System of Units (Système International D'Unités [SI Units])

SI Base Units

Length	meter, m
Mass	kilogram, kg
Time	second, s
Temperature	Kelvin, K
Amount of substance	mole, mol

SI-Derived Units

Area	square meter, m ²
Volume	cubic meter, m ³
Concentration	mole per cubic meter, mol/m ³

Temperature Scales and Temperature Conversions

Scale	Absolute Zero	Freezing (Water)	Boiling (Water)
Kelvin	0°	273°	373°
Centigrade	-273°	0°	100°
Fahrenheit	-460°	32°	212°

Conversion: Centigrade/Fahrenheit

To convert from Fahrenheit to Centigrade:

$$\text{Centigrade (degrees)} = 0.55 \times (\text{Fahrenheit} - 32)$$

To convert from Centigrade to Fahrenheit:

$$\text{Fahrenheit (degrees)} = (1.8 \times \text{Centigrade}) + 32$$

Liquid Metric Conversions

United States		United Kingdom	
1 gallon (gal)	$\equiv$ 3785 mL	1 gallon	$\equiv$ 4546 mL
1 pint (pt)	$\equiv$ 473.18 mL	1 pint	$\equiv$ 568.26 mL
16 fluid ounces	$\equiv$ 473.18 mL	20 fluid ounces	$\equiv$ 568.26 mL
8 fluid ounces	$\equiv$ 236.49 mL	10 fluid ounces	$\equiv$ 284.14 mL
4 fluid ounces	$\equiv$ 118.29 mL	5 fluid ounces	$\equiv$ 142.07 mL
1 fluid ounce	$\equiv$ 29.57 mL	1 fluid ounce	$\equiv$ 28.41 mL

Household/Apothecary

1 tablespoon	$\equiv$ 15 mL (approx.)	
1 teaspoon	$\equiv$ 5 mL (approx.)	
1 cc	$\equiv$ 1 g	$\equiv$ 1 mL (approx.)
15–16 drops (gtt)	$\equiv$ 1 cc	$\equiv$ 1 mL
10 minims	$\equiv$ 0.616 mL	
1 drop	$\equiv$ 1 minim (approximate)	

Note: Spoon and drop conversions should be regarded as approximations because of the different surface tensions and specific gravity of various liquids.

Solid Metric Conversions

Imperial	Metric
Avoirdupois	
1 stone	6.35 kg
2.2 pounds	1 kg
1 pound	453.592 g, 0.45 kg
1 ounce	28.35 g

Apothecary

1 pound	373.242 g
1 ounce	31.10 g
1 dram/drachm	28.8 g
1 scruple	1.2 g
15 grains	1 g
10 grains	600 mg
7 ½ grains	500 mg
5 grains	300 mg
1 ½ grains	100 mg
1 grain	65.79891 mg
½ grain	30 mg
¼ grain	15 mg
⅛ grain	8 mg
⅓ grain	5 mg
1/100 grain	600 mcg
1/150 grain	400 mcg
1/200 grain	300 mcg
1/250 grain	250 mcg
1/300 grain	200 mcg

Household Units

The metric system of measure generally is used for drug amounts. However household measures, such as teaspoons or tablespoons, are used for administering medications in the home environment. For example, a cough syrup may have a label giving a usual adult dose as “1 teaspoon every 6 hours.” Household measures are not consistent; a teaspoon may vary from 3 to 5 mL. Although the

metric system, which is more exact and consistent with milligrams, micrograms, and milliliters, is recommended in place of household measures, the following equivalences may be helpful. Use of household measures, such as teaspoons, can be very helpful in discussing amounts of substances with a patient.

- 1 teaspoon = 5 mL = 60 drops.
- 1 tablespoon = 15 mL (or 3 teaspoons)
- 1 cup = 240 mL (or 8 fluidounces)

Ratios and Percent Solutions

1:100	≡ 1 g/100 mL (10 mg/mL)	≡ 1%
1:200	≡ 500 mg/100 mL (5 mg/mL)	≡ 0.5%
1:1000	≡ 100 mg/100 mL (1 mg/mL)	≡ 0.1%
1:5000	≡ 20 mg/100 mL (200 mcg/mL)	≡ 0.02%
1:10,000	≡ 10 mg/100 mL (100 mcg/mL)	≡ 0.01%

Calculation of Milliequivalents (mEq)

$$\text{mEq} = \frac{\text{Weight in grams}}{\text{mEq Weight in grams}}$$

Ion or Compound	mEq Weight (g)	Ion or Compound	mEq Weight (g)
Magnesium (Mg^{++})	0.012	Bicarbonate (HCO_3^-)	0.061
Ammonium (NH_4^+)	0.018	Citrate	0.063
Calcium (Ca^{++})	0.020	Calcium chloride (CaCl_2) dihydrate	0.0735
Sodium (Na^+)	0.023	Potassium chloride (KCl)	0.0745
Phosphorus	0.031	Sodium bicarbonate (NaHCO_3)	0.084
Chloride (Cl^-)	0.0355	Lactate	0.089
Potassium (K^+)	0.039	Magnesium sulfate (MgSO_4) heptahydrate	0.123
Ammonium chloride (NH_4Cl)	0.0535	Calcium gluconate	0.224
Sodium chloride (NaCl)	0.0585	Acetate	0.059

For milliequivalent weights not shown, use the formula: Milliequivalent weight (mEq W.) = atomic weight (g)/(valence) $\times$ 1000.

Drug Administration Times

Standardized medication administration times should be followed as much as possible. The following table shows the hours of the day that are to be used as standardized times of medication administration. If the prescriber wishes the first dose to be administered before the earliest available standardized time, the prescriber should state “expedite” or “first dose now” with the drug order. In intensive care units, the first dose of a newly ordered parenteral antibiotic regimen should be administered within 2 hours unless specified otherwise by the prescriber.

Ordered Time	Hour(s) to Be Given	Military Time
qam	8:00 AM	0800
qd	8:00 AM	0800
qhs	9:00 PM	0900
qprn	5:00 PM	1700
bid	8:00 AM and 5:00 PM	0800 and 1700
q12h	8:00 AM and 8:00 PM	0800 and 2000
q8h	8:00 AM, 6:00 PM, and 12:00 AM	0800, 1800, and 2400
tid	8:00 AM, 12:00 PM, and 5:00 PM	0800, 1200, and 1700
tid ac	7:00 AM, 12:00 PM, and 5:00 PM	0700, 1200, and 1700
tid w/m	7:30 AM, 12:30 PM, and 5:30 PM	0730, 1230, and 1730
qid	8:00 AM, 12:00 PM, 5:00 PM, and 9:00 PM	0800, 1200, 1700, and 2100
q6h	6:00 AM, 12:00 PM, 6:00 PM, and 12:00 AM	0600, 1200, 1800, and 2400
ac and hs	7:00 AM, 12:00 PM, 5:00 PM, and 9:00 PM	0700, 1200, 1700, and 2100
pc and hs	8:00 AM, 1:00 PM, 6:00 PM, and 9:00 PM	0800, 1300, 1800, and 2100
1 hr ac and hs	6:30 AM, 11:30 AM, 4:30 PM, and 9:00 PM	0630, 1130, 1630, and 2100
1 hr pc and hs	8:30 AM, 1:30 PM, 6:30 PM, and 9:00 PM	0830, 1330, 1830, and 2100
5 $\times$ /day	6:00 AM, 10:30 AM, 3:00 PM, 7:30 PM, and 11:00 PM	0600, 1030, 1500, 1930, and 2300
q4h	4:00 AM, 8:00 AM, 12:00 PM, 4:00 PM, 8:00 PM, and 12:00 AM	0400, 0800, 1200, 1600, 2000, and 2400

Estimating Lean Body Weight

Lean Body Weight Calculation

Males: 50 kg + 2.3 kg per each inch over 5 feet of height

Females: 45 kg + 2.3 kg per each inch over 5 feet of height

Height		Estimated Lean Body Weight		Height		Estimated Lean Body Weight	
Imperial	Metric	Males (kg)	Females (kg)	Imperial	Metric	Males (kg)	Females (kg)
4 ft 8 in	142 cm	40.8	36.3	5 ft 9 in	175 cm	70.7	66.2
4 ft 9 in	145 cm	43.1	38.6	5 ft 10 in	178 cm	73.0	68.5
4 ft 10 in	147 cm	45.4	40.9	5 ft 11 in	180 cm	75.3	70.8
4 ft 11 in	150 cm	47.7	43.2	6 ft 0 in	183 cm	77.6	73.1
5 ft 0 in	152 cm	50.0	45.5	6 ft 1 in	185 cm	79.9	75.4
5 ft 1 in	155 cm	52.3	47.8	6 ft 2 in	188 cm	82.2	77.7
5 ft 2 in	157 cm	54.6	50.1	6 ft 3 in	191 cm	84.5	80.0
5 ft 3 in	160 cm	56.9	52.4	6 ft 4 in	193 cm	86.8	82.3
5 ft 4 in	163 cm	59.2	54.7	6 ft 5 in	196 cm	89.1	84.6
5 ft 5 in	165 cm	61.5	57.0	6 ft 6 in	198 cm	91.4	86.9
5 ft 6 in	168 cm	63.8	59.3	6 ft 7 in	201 cm	93.7	89.2
5 ft 7 in	170 cm	66.1	61.6	6 ft 8 in	203 cm	96.0	91.5
5 ft 8 in	173 cm	68.4	63.9				

Appendix C

Acceptable Mixtures of Most Commonly Prescribed Respiratory Care Drugs

TABLE C.1 Admixture Advices for Commonly Used Drug Solutions/Suspensions in Nebulizers

	Albuterol	Ipratropium	Cromolyn	Budesonide	Tobramycin	Colistin	Dornase Alfa
Albuterol/ Levalbuterol	Not applicable	Possible*	Possible*	Possible*	Possible*	Possible*	Not recommended
Ipratropium	Possible*	Not applicable	Possible*	Possible*	Possible*	No information	Not recommended
Cromolyn	Possible*	Possible*	Not applicable	Possible*	Not recommended	No information	Not recommended
Budesonide	Possible*	Possible*	Possible*	Not applicable	Not recommended	No information	Not recommended
Tobramycin	Possible*	Possible*	Not recommended	Not recommended	Not applicable	No information	Not recommended
Colistin	Possible*	No information	No information	No information	Not reasonable	Not applicable	Not recommended
Dornase alfa	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not applicable

*Mixtures are compatible, if preservative-free solutions (no benzalkonium chloride) are used.

From Kamin, W., Erdnuss, F., & Kramer, I. (2014). Inhalation solutions—which ones may be mixed? Physico-chemical compatibility of drug solutions in nebulizers—update 2013. *Journal of Cystic Fibrosis*, 13(3), 243–250.

Glossary of Selected Terms

An eclectic glossary of the terms encountered in pharmacology, many from the basic sciences, is offered for convenience in using the text as a study source. This glossary is not intended to substitute for a comprehensive dictionary of medical terms. Selection of terms for inclusion is based on the author's experience in reading the literature of drug actions and effects. Terms that are frequently found or used in discussing drugs but may be less well known to the practicing clinician are included.

A

Abhesives Coating that reduces adhesion. (Chapter 9)

Acetylcholine (ACh) Chemical that is produced by the body and is used in transmission of nerve impulses. It is destroyed by the enzyme cholinesterase. (Chapter 5)

Acetylcholinesterase (AChE) Enzyme that breaks down the neurotransmitter acetylcholine at the synaptic cleft so that the next nerve impulse can be transmitted across the synaptic gap. (Chapter 18)

Acute respiratory distress syndrome (ARDS) Respiratory disorder characterized by respiratory insufficiency. This disorder may occur as a result of trauma, pneumonia, oxygen toxicity, gram-negative sepsis, or systemic inflammatory response. (Chapter 1)

Adrenal cortical hormones Chemicals secreted by the adrenal cortex. An adrenal cortical hormone is also referred to as a steroid. (Chapter 11)

Adrenergic (adrenomimetic) Refers to a drug stimulating a receptor for norepinephrine or epinephrine. (Chapter 5)

Adrenergic bronchodilator Agent that stimulates sympathetic nervous fibers, which allow relaxation of smooth muscle in the airway. Also known as a *sympathomimetic bronchodilator* or *β_2 agonist*. (Chapter 6)

Aerodynamic diameter of a particle Diameter of a unit-density (1 g/cc) spherical particle having the same terminal settling velocity as the measured particle. (Chapter 3)

Aerosol Suspension of liquid or solid particles, between 0.001 and 100 micrometers (μm) in diameter, in a carrier gas. (Chapter 3)

Aerosol therapy Delivery of aerosol particles to the lungs. (Chapter 3)

Aerosolized agents Group of aerosol drugs for pulmonary applications that includes adrenergic, anticholinergic, mucocactive, corticosteroid, antiasthmatic, and antiinfective agents and surfactants instilled directly into the trachea. (Chapter 1)

Afferent Signals that are transmitted to the brain and spinal cord. (Chapter 5)

Agonist Chemical or drug that binds to a receptor and creates an effect on the body. (Chapter 2)

Airway resistance (R_{aw}) Measure of impedance to ventilation caused by movement of gas through the airway. (Chapter 1)

Alkaloids Group of alkaline substances taken from plants, which react with acids to form salts (e.g., theophylline). (Chapter 8)

α_1 -Antitrypsin (α_1 -AT) Inhibitor of trypsin that may be deficient in patients with emphysema. Also known as *α_1 -proteinase inhibitor (API)*. (Chapter 16)

α -Receptor stimulation Causes vasoconstriction and vasopressor effect; in the upper airway (nasal passages), this can provide decongestion. (Chapter 6)

Amnesic properties Having the ability to cause total or partial loss of memory. (Chapter 18)

Analgesics Drugs that provide pain relief. Analgesics can be subdivided into narcotic and nonnarcotic medications. Narcotic drugs are derivatives of opium, such as morphine and codeine. Nonnarcotic medications are useful in treating pain and inflammation. They also have antipyretic activity. (Chapter 20)

Anesthetics Drugs that depress the nervous system. Anesthetics can be divided into local and general anesthetics. *General anesthetics* cause total loss of consciousness and reflexes, which results in the absence of pain perception. *Local anesthetics* are applied to a specific site, decrease pain perception at the specific site, and do not affect level of consciousness. Both types of anesthetics are often used during surgical procedures. (Chapter 20)

Antagonism Antibiotic combination in which the activity of one antibiotic interferes with the activity of the other (block receptor site, enzymatic inactivation), resulting in less activity with the combination than with the individual drugs (i.e., $1 + 1 < 1$). (Chapter 14)

Antagonist Chemical or drug that binds to a receptor but does not create an effect on the body; it actually blocks the receptor site from accepting an agonist. (Chapter 2)

Antidrenergic Refers to a drug blocking a receptor for norepinephrine or epinephrine. (Chapter 5)

Antiarrhythmics Group of cardiac medications that are classified according to mechanism of action; in some instances, they may have multiple mechanisms of action. The most common classification system of antiarrhythmics is the Vaughan Williams classification system, which is divided into four distinct categories and a miscellaneous section. (Chapter 21)

Antibiotics Substance derived or produced from a microorganism that inhibits or kills other microorganisms. (Chapter 14)

Anticholinergic Refers to a drug blocking a receptor for acetylcholine. (Chapter 5)

Anticholinergic bronchodilator Agent that blocks parasympathetic nervous fibers, which allows relaxation of smooth muscle in the airway. (Chapter 7)

Antidepressants Drugs that can alter levels of certain neurotransmitters, in particular norepinephrine

and serotonin, within the brain. Depending on the class of antidepressant, they can either inhibit the reuptake of neurotransmitters or decrease their degradation, ultimately allowing for increased levels of neurotransmitter at the nerve terminal. (Chapter 20)

Antihistamines Drugs that reduce the effects mediated by histamine, a chemical released by the body during allergic reactions. Antihistamine is often administered to reduce secretions (e.g., runny nose and sneezing), but they can cause drowsiness and impaired responses. (Chapter 15)

Antileukotrienes Agents that blocks the inflammatory response in asthma. (Chapter 12)

Antimicrobials Natural and synthetic compounds that either inhibit or kill microorganisms. (Chapter 14)

Antimuscarinic bronchodilator Same as an *anticholinergic bronchodilator*: an agent that blocks the effect of acetylcholine at the cholinergic site. (Chapter 7)

Antipsychotics Drugs used to treat psychotic disorders, such as schizophrenia. These drugs primarily affect the neurotransmitter dopamine. (Chapter 20)

Antithrombotics Drug that prevents or breaks up blood clots in such conditions as thrombosis or embolism; antithrombotics include anticoagulants, antiplatelets, and thrombolytics. (Chapter 22)

Antitussives Drugs that suppress the cough reflex. *Note*: Productive coughs should not be suppressed; the logic of an expectorant-antitussive combination is questionable. (Chapter 15)

Anxiolytics Drugs used to treat several conditions, including anxiety disorders and insomnia; also known as *minor tranquilizers*. The most common class of anxiolytics is the benzodiazepines. They bind to the γ -aminobutyric acid receptor to increase the inhibitory actions of this neurotransmitter. (Chapter 20)

API deficient Refers to an individual who has low serum levels of α_1 -proteinase inhibitor (API) possessing altered electrophoretic properties. (Chapter 16)

API dysfunctional Refers to an individual who has normal serum levels of API that does not function normally. (Chapter 16)

API normal Refers to an individual who has normal serum levels of API that functions normally. (Chapter 16)

API null Refers to an individual who has undetectable serum levels of API. (Chapter 16)

Arrhythmias/dysrhythmias Irregular (faster or slower) heartbeat; the term *arrhythmia* is used more frequently than *dysrhythmia*. (Chapter 21)

Arterial blood pressure (blood pressure) Defined hemodynamically as the product of cardiac output (heart rate $\times$ stroke volume) and total peripheral resistance. (Chapter 22)

Aspiration Accidental inhalation of food particles, fluids, or gastric contents into the lungs. (Chapter 18)

Asthma paradox Refers to the increasing incidence of asthma morbidity and especially asthma mortality, despite advances in the understanding of asthma and availability of improved drugs to treat asthma. (Chapter 6)

Atrioventricular (AV) node Link between atrial depolarization and ventricular depolarization. (Chapter 21)

B

Barbiturates Compounds whose parent structure is uric acid. These compounds depress central nervous system activity. Long-acting barbiturates such as pentobarbital have been used to treat epilepsy. Barbitals were used during the early twentieth century to facilitate sleep in individuals with insomnia. (Chapter 23)

Benzodiazepines Compounds whose parent structure is a fusion of a diazepine ring with a benzene ring. Benzodiazepines enhance activity of the inhibitory neurotransmitter γ -aminobutyric acid. Benzodiazepines, which reduce anxiety and promote muscle relaxation, also promote sleep. The earliest benzodiazepines were chlordiazepoxide (Librium) and diazepam (Valium). Benzodiazepines for insomnia are now being replaced by nonbenzodiazepines, such as zolpidem (Ambien) and eszopiclone (Lunesta). (Chapter 23)

β_1 -Receptor stimulation Causes increased myocardial conductivity and increased heart rate and increased contractile force. (Chapter 6)

β_2 -Receptor stimulation Causes relaxation of bronchial smooth muscle, with some inhibition of inflammatory mediator release and stimulation of mucociliary clearance. (Chapter 6)

Bioavailability Amount of drug that reaches the systemic circulation. (Chapter 2)

Bohr effect Presence of carbon dioxide aiding in the release and delivery of oxygen from hemoglobin. (Chapter 21)

Brand name See *Trade name*. (Chapter 1)

Bronchospasm Narrowing of the bronchial airways caused by contraction of smooth muscle. (Chapter 6)

C

Cardiac output (CO) Amount of blood that is ejected into the aorta and travels through the systemic circulation with every heartbeat. (Chapter 21)

Cardiovascular disease (CVD) Damage to the heart and blood vessels or circulation, including circulation to the brain, kidney, and eyes. (Chapter 22)

Cascade impactor Device that uses multiple steps in determining aerosol particle sizes. (Chapter 3)

Catecholamines Group of similar compounds having sympathomimetic action; they mimic the actions of epinephrine. (Chapter 6, Chapter 21)

Central nervous system (CNS) System that includes the brain and spinal cord, controlling voluntary and involuntary acts. The brain and spinal cord make up the functional components of the CNS. The spinal cord provides nerve fibers that transport signals to and from the brain. The brain largely comprises three components: cortex, midbrain, and brainstem. (Chapter 5, Chapter 20)

Chemical name Name indicating the chemical structure of a drug. (Chapter 1)

Chlorofluorocarbon (CFC) Liquefied gas (e.g., Freon) propellant used to administer medication from a metered dose inhaler (MDI). (Chapter 3)

Cholinergic (cholinomimetic) Parasympathomimetic agents causing stimulation of a receptor for acetylcholine. (Chapter 5, Chapter 7)

Cholinesterase inhibitors Drugs that block the activity of cholinesterase, an enzyme that inactivates the neurotransmitter acetylcholine. Acetylcholine is found at nerve terminals in both the central and the peripheral nervous systems. Cholinesterase inhibitors are used in the treatment of dementia to slow the progression of cognitive decline. (Chapter 20)

Chronic obstructive pulmonary disease (COPD) Disease process characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lung to noxious particles or gases. Diseases that cause airflow limitation include chronic bronchitis, emphysema, asthma, and bronchiectasis. (Chapter 1)

Chronotropic Agent affecting the rate of contraction of the heart. (Chapter 21, Chapter 22)

Circadian rhythm The approximately 24-hour cycle of biochemical, physiologic, and behavioral processes. *Circa* is Latin for "about," and *diem* is Latin for "day." (Chapter 22, Chapter 23)

Code name Name assigned by a manufacturer to an experimental chemical that shows potential as a drug. An example is aerosol SCH 1000, which was the code name for ipratropium bromide, a parasympatholytic bronchodilator. (Chapter 1)

Common cold Nonbacterial respiratory tract infection characterized by malaise and a runny nose. (Chapter 15)

Congestive heart failure (CHF) Failure of the heart to pump blood adequately, resulting in lung congestion and tissular edema. (Chapter 19)

Conscious sedation Method of sedation used during certain invasive procedures. The goals of conscious sedation are to decrease the level of consciousness and relieve anxiety and pain, while allowing the patient to follow verbal commands. Conscious sedation is achieved through the use of several classes of drugs, including benzodiazepines and narcotic analgesics. (Chapter 20)

Creatinine clearance Measurement of the renal clearance of endogenous creatinine per unit of time; considered to be an estimate of glomerular filtration rate (GFR) but overestimates GFR by 10% to 15%. It is used for drug-dosing guidelines. (Chapter 22)

Cyclic AMP (cAMP) Nucleotide produced by β_2 -receptor stimulation; it affects many cells but causes relaxation of bronchial smooth muscle. (Chapter 6)

Cyclic GMP (cGMP) Nucleotide producing the opposite effect of cAMP; that is, it causes bronchoconstriction. (Chapter 6)

Cystic fibrosis (CF) Inherited disease of the exocrine glands, affecting the pancreas, respiratory system, and apocrine glands. Symptoms usually begin in infancy and are characterized by increased electrolytes in the sweat, chronic respiratory infection, and pancreatic insufficiency. (Chapter 1, Chapter 13)

D

d-Dimers Covalently cross-linked degradation fragments of the cross-linked fibrin polymer during plasmin-mediated fibrinolysis; the level increases after the onset of fibrinolysis and allows for identification of the presence of fibrinolysis. (Chapter 22)

Dead volume Amount of solution that remains in the reservoir of a small volume nebulizer once sputtering begins, causing a decrease in aerosolization. (Chapter 3)

Deposition Process by which particles deposit out of suspension to remain in the lung. (Chapter 3)

Diastolic blood pressure (DBP) Lowest pressure reached right before ventricular ejection. (Chapter 21)

Diuretics Drug that increases urine output. (Chapter 19)

Dose-ceiling effect Maximum dose of a drug beyond which it no longer exerts a therapeutic effect; however, toxic effects increase. (Chapter 22)

Downregulation Long-term desensitization of β receptors to β_2 agonists caused by a reduction in the number of β receptors. (Chapter 6)

Dromotropic An agent that influences the conduction of electrical impulses. A positive dromotropic agent enhances the conduction of electrical impulses to the heart. (Chapter 21)

Drug administration Method by which a drug is made available to the body. (Chapter 1, Chapter 2)

Dysrhythmia/arrhythmia Irregular (faster or slower) heartbeat; the term *arrhythmia* is used more frequently than *dysrhythmia*. (Chapter 21)

E

Edema Swelling resulting from abnormal accumulation of fluid in intercellular spaces of the body. (Chapter 19)

Efferent Signals that are transmitted from the brain and spinal cord. (Chapter 5)

Elasticity Rheologic property characteristic of solids; it is represented by the storage modulus G' . (Chapter 9)

Electroencephalography (EEG) Measurement and recording of the gross electrical activity of the brain. During EEG recordings, electrodes are typically placed across multiple scalp regions. The electrodes are connected to amplifiers and filters that detect, magnify, and record the electrical activity of the brain. (Chapter 23)

Emitted dose Dose released by an aerosol device. (Chapter 17)

Endogenous Refers to *inside*, produced by the body. (Chapter 11)

Enteral Use of the intestine. (Chapter 2)

Exogenous Refers to *outside*, manufactured to be placed inside the body (e.g., medication). (Chapter 11)

Expectorants Medication meant to increase the volume or hydration of airway secretions. (Chapter 9, Chapter 15)

F

Fasciculation Involuntary contraction or twitching of groups of muscle fibers. (Chapter 18)

Fibrin split or fibrinogen degradation products (FDPs) Small peptides that result after the action of plasmin on fibrinogen and fibrin in the fibrinolytic process. FDPs are anticoagulant substances that can cause bleeding if fibrinolysis becomes uncontrolled and excessive. (Chapter 22)

First-pass effect Initial metabolism in the liver of a drug taken orally, before the drug reaches the systemic circulation. (Chapter 2)

Flu Nonbacterial infection with rapid onset of symptoms, including fever, headache, and fatigue. (Chapter 15)

G

Gel Macromolecular description of pseudoplastic material having both viscosity and elasticity. (Chapter 9)

Generic name Name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug. (Chapter 1)

Glomerular filtration Mechanism by which hydrostatic pressure forces fluid out of the glomerular capillaries and into the renal ducts. (Chapter 19)

Glomerular filtration rate (GFR) Volume of water filtered from the plasma by the kidney via the glomerular capillary walls into Bowman capsules per unit time; considered to be 90% of creatinine clearance and equivalent to inulin clearance. (Chapter 22)

Glycoproteins Protein with covalently attached oligosaccharide units. The principal constituent of mucus and a high-molecular-weight glycoprotein, it gives mucus its physical and chemical properties, such as viscoelasticity. (Chapter 9)

H

Heterodisperse In reference to the size of particles in an aerosol, meaning the particles are of different sizes. (Chapter 3)

Hydrofluoroalkane (HFA) Nontoxic liquefied gas propellant used to administer medication from an MDI. (Chapter 3)

Hypersensitivity Allergic or immune-mediated reaction to a drug, which can be serious, requiring airway maintenance or ventilatory assistance. (Chapter 2)

Hypersomnia Presence of excessive sleepiness. Daytime sleepiness is so great that it leads to inappropriate daytime napping or sleep. Excessive sleepiness is not alleviated by prolonged sleep times or by napping. (Chapter 23)

Hypertensive emergency Blood pressures greater than 180/120 mm Hg, when the elevation of blood pressure is accompanied by acute, chronic, or progressing target organ injury. (Chapter 22)

Hypertensive urgency Blood pressures greater than 180/120 mm Hg without signs or symptoms of acute target organ complications. (Chapter 22)

Hypnotic Class of drugs used to induce sleep. (Chapter 23)

Hypovolemia Abnormally decreased volume of blood circulating in the body. (Chapter 19)

I

Idiosyncratic effect Abnormal or unexpected reaction to a drug, other than an allergic reaction, compared with the predicted effect. (Chapter 2)

Immunoglobulin E (IgE) Gamma globulin that is produced by cells in the respiratory tract. (Chapter 11, Chapter 12)

In vitro Mechanically simulating the clinical setting; testing in a laboratory. (Chapter 3)

In vivo Testing done on animals or humans; clinical testing. (Chapter 3)

Infant Child between the ages of 1 month and 1 year. (Chapter 17)

Inhalation Taking a substance, typically in the form of gases, fumes, vapors, mists, aerosols, or dusts, into the body by breathing in. (Chapter 2)

Inhaled (delivered) dose Dose reaching the patient's mouth or artificial airway. (Chapter 17)

Inotropic Agents affecting the strength of muscular contraction. (Chapter 21, Chapter 22)

Intrinsic sympathomimetic activity (ISA) Having the ability to activate and block adrenergic receptors, producing a net stimulatory effect on the sympathetic nervous system. (Chapter 22)

L

Laplace's law Physical principle describing and quantifying the relationship between the internal pressure of a drop or bubble, the amount of surface tension, and the radius of the drop or bubble. (Chapter 10)

Leukotrienes Chemical mediators that cause inflammation. (Chapter 12)

Local effect Limited to the area of treatment (e.g., inhaled drug to treat constricted airways). (Chapter 2)

Lung availability/total systemic availability ratio (L/T ratio) Amount of drug that is made available to the lung out of the total available to the body. (Chapter 2)

Lung dose Dose reaching the trachea and beyond. (Chapter 17)

M

Mast cells Connective tissue cells that contain heparin and histamine. (Chapter 12)

Mast cell stabilizers Also known as *cromolyn-like agents*; agents used prophylactically to treat the inflammatory response in asthma. (Chapter 12)

Mean arterial pressure (MAP) Pressure that drives blood into the tissues averaged over the entire cardiac cycle. (Chapter 21)

Methylxanthines Chemical group of drugs derived from xanthines. There are three methylated (CH₃) xanthines: caffeine, theophylline, and theobromine. (Chapter 8)

Monodisperse In reference to the size of particles in an aerosol, meaning all particles are the same size. (Chapter 3)

Mood stabilizers Drugs used primarily to treat bipolar disorders. (Chapter 20)

Mucins Principal constituent of mucus. Principal airway gel-forming mucins MUC2, MUC5AC, and MUC5B are proteins with attached oligosaccharide (sugar) side chains. (Chapter 9)

Mucoactive agent Term connoting any medication or drug that has an effect on mucus secretion. See *Mucokinetic agent*, *Mucolytic agent*, *Mucolytic expectorant*, *Mucoregulatory agent*, and *Mucospissic agent*. (Chapter 9)

Mucokinesis Therapeutic movement of excessive or abnormal secretions from the respiratory tract. (Chapter 15)

Mucokinetic agents Medication that increases ciliary clearance of respiratory mucus secretions. (Chapter 9)

Mucolytic agent Medication that degrades polymers in secretions. *Classic mucolytics* have free thiol groups to degrade mucin, and *peptide mucolytics* break pathologic filaments of neutrophil-derived DNA or actin in sputum. Classic mucolytics are ineffective for the therapy of airway disease and are not recommended, whereas dornase alfa seems to be effective for the therapy of cystic fibrosis and perhaps bronchiectasis. (Chapter 9)

Mucolytic expectorants Agent that facilitates removal of mucus by a lysing, or mucolytic, action. *Example:* dornase alfa. (Chapter 15)

Mucoregulatory agent Drug that reduces the volume of airway mucus secretion and seems to be especially effective in hypersecretory states, such as bronchorrhea, diffuse panbronchiolitis, cystic fibrosis, and some forms of asthma. (Chapter 9)

Mucospissic agents Medication that increases the viscosity of secretions and may be effective in the therapy of bronchorrhea. (Chapter 9)

Mucus Secretion, from surface goblet cells and submucosal glands, composed of water, proteins, and glycosylated mucins. The glycoprotein portion of the secretion is termed *mucin*. *Mucus* (noun) is the secretion; *mucous* (adjective) is the cell or gland type. (Chapter 9)

Muscarinic An agent that produces the effect of acetylcholine or an agent that mimics acetylcholine. Same as *cholinergic*. (Chapter 7)

Myasthenia gravis Autoimmune neuromuscular disorder characterized by chronic fatigue and exhaustion of muscles. (Chapter 18)

N

Nebulizer Device used for making a fine spray or mist, also known as an *aerosol generator*. (Chapter 3)

Neonatal Refers to period of time between birth and first month of life. (Chapter 17)

Nephrocalcinosis Renal lithiasis in which calcium deposits form in the renal parenchyma, resulting in reduced kidney function and the presence of blood in the urine. (Chapter 19)

Nephron Microscopic functional unit of the kidney, responsible for filtering and maintaining fluid balance. Each kidney has approximately 2 million nephrons. (Chapter 19)

Nerve cell (neuron) Basic functional unit of the nervous system that is specialized to transmit electrical nerve impulses and carry information from one part of the body to another. A neuron consists of a cell body, axons, and dendrites. (Chapter 18)

Neuromuscular blocking agents (NMBA) Substance that interferes with the neural transmission between motor neurons and skeletal muscles. (Chapter 18)

Neurotransmitter Chemical that is released from a nerve ending to transmit an impulse from a nerve cell to another nerve, muscle, organ, or other tissue, such as *acetylcholine* or *norepinephrine*. (Chapter 18, Chapter 20)

Nominal dose Dose in a delivery device. (Chapter 17)

Nonproprietary name Name of a drug other than its trademarked name. (Chapter 1)

Norepinephrine (NE) Naturally occurring catecholamine produced by the adrenal medulla that has properties similar to epinephrine. It is used as a neurotransmitter in most sympathetic terminal nerve sites. (Chapter 5)

Nosocomial pneumonia Pneumonia that is acquired in a health care setting. (Chapter 18)

O

Official name In the event that an experimental drug becomes fully approved for general use and is admitted to the *United States Pharmacopeia–National Formulary*, the generic name becomes the official name. (Chapter 1)

Off-label Use of drugs with no US Food and Drug Administration (FDA)–approved labeling. (Chapter 17)

Oligosaccharide Sugar that is the individual carbohydrate unit of glycoproteins. (Chapter 9)

Orphan drug Drug or biologic product for the diagnosis or treatment of a rare disease (affecting fewer than 200,000 persons in the United States). (Chapter 1)

Ototoxicity Damage to the ear, specifically the cochlea or auditory nerve and sometimes the vestibulum, by a toxin. (Chapter 19)

P

Parasomnia Group of sleep disorders manifested by undesirable motor, sensory, or behavioral phenomena that occur during sleep. The *International Classification of Sleep Disorders, Revised (ICSD-R)* lists 24 parasomnias. More commonly encountered parasomnias include confusional arousals, sleep terrors, and sleepwalking. (Chapter 23)

Parasympatholytic Agent blocking or inhibiting the effects of the parasympathetic nervous system. (Chapter 5, Chapter 7)

Parasympathomimetic Agent causing stimulation of the parasympathetic nervous system. (Chapter 5, Chapter 7)

Parenteral Administration in any way other than by the intestine; most commonly used to describe injection (e.g., intravenous, intramuscular, or subcutaneous). (Chapter 2)

Pediatric Refers to period between 1 month and 18 years of age. (Chapter 17)

Penetration Refers to the depth within the lung reached by particles. (Chapter 3)

Percent Part of the active ingredient that is in a solution containing 100 parts. (Chapter 4)

Peripheral nervous system (PNS) Portion of the nervous system outside the CNS, including sensory, sympathetic, and parasympathetic nerves. (Chapter 5)

Pharmacodynamics Mechanisms of drug action by which a drug molecule causes its effect in the body. (Chapter 1, Chapter 2)

Pharmacogenetics Study of the interrelationship of genetic differences and drug effects. (Chapter 1, Chapter 2)

Pharmacognosy Identification of sources of drugs from plants and animals. (Chapter 1)

Pharmacokinetics Time course and disposition of a drug in the body based on its absorption, distribution, metabolism, and elimination. (Chapter 1, Chapter 2)

Pharmacology Study of drugs (chemicals), including their origin, properties, and interactions with living organisms. (Chapter 1)

Pharmacotherapy Treatment of disease by drug therapy. (Chapter 22)

Pharmacy Preparation and dispensing of drugs. (Chapter 1)

Phlegm Purulent material in the airways. From the Greek word for inflammation. When expectorated, phlegm is called *sputum*. (Chapter 9)

Phosphodiesterase Enzyme responsible for the breakdown of cyclic adenosine 3',5'-monophosphate (cAMP). (Chapter 8, Chapter 21)

***Pneumocystis jiroveci* (formerly *carinii*)** Organism causing *Pneumocystis* pneumonia in humans, seen in immunosuppressed individuals such as patients with human immunodeficiency virus infection. (Chapter 1)

***Pneumocystis pneumonia* (PCP)** Interstitial plasma cell pneumonia caused by the organism *Pneumocystis carinii* (now known as *Pneumocystis jiroveci*). This pneumonia is common among patients with lowered immune system response. (Chapter 13)

Polydisperse In reference to the size of particles in an aerosol, meaning many different particle sizes. (Chapter 3)

Polysomnography Measurement and recording of EEG activity during sleep, typically coupled with measurement and recording of cardiorespiratory activity and eye movements. (Chapter 23)

Prescription Written order for a drug, along with any specific instructions for compounding, dispensing, and taking the drug. This order may be written by a physician, osteopath, dentist, veterinarian, and other health care providers but not by chiropractors or opticians. (Chapter 1)

Prodrug Drug that exhibits its pharmacologic activity when it is converted, inside the body, to its active form. (Chapter 6)

Prophylactic treatment Prevention of respiratory distress syndrome (RDS) in infants with very low birth weight and in infants with higher birth weight but with evidence of immature

lungs who are at risk for developing RDS. (Chapter 10)

Prostaglandins One of several hormone-type substances circulating throughout the body. (Chapter 11)

Pseudomonas aeruginosa Gram-negative organism, primarily a nosocomial pathogen. It causes urinary tract infections, respiratory system infections, dermatitis, soft tissue infections, bacteremia, bone and joint infections, gastrointestinal infections, and various systemic infections, particularly in patients with severe burns and in patients who are immunosuppressed (e.g., patients with cancer or acquired immunodeficiency syndrome). (Chapter 1)

R

Reabsorption Return to the blood of most of the water, sodium, amino acids, and sugar that were removed during filtration; occurs mainly in the proximal tubule of the nephron. (Chapter 19)

Receptor Molecular structure inside or outside the cell component that combines with a drug to change or enhance the function of the cell. (Chapter 2, Chapter 18)

Renin Enzyme, also known as *angiotensinogenase*, released by the kidney in response to a lack of renal blood flow and responsible for converting angiotensinogen into angiotensin I. (Chapter 22)

Rescue treatment Retroactive, or "rescue," treatment of infants who have developed respiratory distress syndrome. (Chapter 10)

Reservoir device Global term describing or referring to extension, auxiliary, or add-on devices attached to MDIs for administration of medication. This term can include *spacer* and *valved holding chamber*. (Chapter 3)

Respiratory care pharmacology Application of pharmacology to the treatment of pulmonary disorders and more broadly, critical care. (Chapter 1)

Respiratory syncytial virus (RSV) Virus that causes the formation of syncytial masses in cells. This leads to inflammation of the bronchioles, which may cause respiratory distress in infants. (Chapter 1, Chapter 13)

Rheology Study of the deformation and flow (strain) of matter. (Chapter 9)

S

Schedule Amount of drug that is needed, based on a patient's weight. (Chapter 4)

Sedation Production of a restful state of mind, particularly by the use of drugs that have a calming effect, relieving anxiety and tension. (Chapter 18)

Sol Macromolecular description of the respiratory secretion in true solution, with the physical property of viscosity (usually referred to as the *periciliary layer*). (Chapter 9)

Solute Substance or active ingredient that is dissolved in a solution. (Chapter 4)

Solution Physically homogeneous mixture of two or more substances (liquid). *Buffer solution* refers to an aqueous solution able to resist changes of pH with addition of acid or base. *Isotonic solution* refers to a solution having equal concentrations inside and outside the cell. *Normal solution* refers to 1 gram-equivalent weight of solute per 1 L of solution. *Molal solution* refers to 1 mole of solute per 1000 g of solvent. *Molar solution* refers to 1 mole of solute per 1 L of solution. *Osmolal solution* refers to 1 osmole per kilogram of solvent. *Osmolar solution* refers to 1 osmole per liter of solution. (Chapter 4)

Solvent Substance, usually a liquid, used to make a solution. (Chapter 4)

Somatic motor neurons Part of the nervous system that controls muscles that are under voluntary control. (Chapter 18)

Spacer Simple tube or extension device with no one-way valves to contain the aerosol cloud; its purpose is simply to extend the MDI spray away from the mouth. (Chapter 3)

Sputum Expectorated secretions that contain respiratory tract, oropharyngeal, and nasopharyngeal secretions; bacteria; and products of inflammation, including polymeric DNA and actin. Purulent sputum contains very little mucin and is similar in composition to pus. (Chapter 9)

Stability Describing the tendency of aerosol particles to remain in suspension. (Chapter 3)

Status asthmaticus Exacerbation of asthma that does not respond to standard treatment. (Chapter 18)

Status epilepticus At least 30 minutes of continuous seizure activity without full recovery between seizures. (Chapter 18)

Steroid diabetes Hyperglycemia (i.e., increased plasma glucose levels) resulting from glucocorticoid therapy; glucocorticoids break down proteins and fats to generate building blocks for gluconeogenesis. (Chapter 11)

Steroids Also known as *glucocorticoid* or *corticosteroid*; an agent that produces an antiinflammatory response in the body. (Chapter 11)

Stimulant Drug that increases activity of the brain. Stimulants can be divided into two classes: amphetamines and respiratory stimulants. Amphetamines cause increased wakefulness, improved concentration, and appetite suppression. Respiratory stimulants include doxapram, xanthines, carbonic anhydrase inhibitors, salicylates, and progesterone. (Chapter 20)

Stimulant expectorants Agent that increases the production and presumably the clearance of mucus secretions in the respiratory tract. *Example:* guaifenesin. (Chapter 15)

Strength Amount of solute in a solution, usually expressed as a percentage. (Chapter 4)

Structure-activity relationship (SAR) Relationship between a drug's chemical structure and the outcome it has on the body. (Chapter 2)

Substitute neurotransmitter Neurotransmitter or hormone replacement that may be weaker or inert. (Chapter 22)

Sudden cardiac death (SCD) Episode of ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, or asystole. (Chapter 21)

Surface tension Attraction of molecules in a liquid-air interface, such as the liquid lining in lung tissue and the air, pulling the surface molecules inward. (Chapter 10)

Surfactants Agent that reduces surface tension. (Chapter 10)

Sympatholytic Agent blocking or inhibiting the effect of the sympathetic nervous system. (Chapter 5)

Sympathomimetics Drugs that partially or completely mimic the effects of the sympathetic nervous system. *Note:* Tremor, tachycardia, and increased blood pressure can occur with their use, especially when taken orally. Rebound congestion can occur if used for longer than 1 day. (Chapter 5, Chapter 6, Chapter 15)

Synergism Drug interaction that occurs from combined drug effects that are greater than if the drugs were given alone. (Chapter 2)

Synergistic effect Effect of two chemicals on an organism is greater than the effect of either chemical individually. (Chapter 19)

Synergy Combined effect of two antimicrobials is greater than their added effect (i.e., $1 + 1 > 2$). (Chapter 14)

Systemic effect Pertains to the whole body, whereas the target for the drug is not local;

possibly causing side effects (e.g., capsule of acetaminophen for a headache). (Chapter 2)

Systolic blood pressure (SBP) Peak pressure reached during ventricular ejection. (Chapter 21)

T

Tachycardia Overly rapid heartbeat, usually defined as greater than 100 beats/min in adults. (Chapter 21)

Tachyphylaxis Rapid decrease in response to a drug. (Chapter 2)

Therapeutic index (TI) Difference between the minimal therapeutic and toxic concentrations of a drug; the smaller the difference, the greater chance the drug would be toxic. (Chapter 2)

Therapeutics The art of treating disease with drugs. (Chapter 1)

Tolerance Decreasing intensity of response to a drug over time. (Chapter 2)

Topical In pharmacology, use of the skin or mucous membrane for drug administration (e.g., lotion). (Chapter 2)

Toxicology Study of toxic substances and their pharmacologic actions, including antidotes and poison control. (Chapter 1)

Trade name Brand name, or proprietary name, given by a particular manufacturer. (Chapter 1)

Transdermal Use of the skin for drug administration (e.g., patch). (Chapter 2)

U

Urine output Amount of urine produced in 24 hours. Normal urine output averages 30 to 60 mL/hr. (Chapter 19)

V

Valved holding chamber Spacer device with the addition of one-way valve to contain and hold the aerosol cloud until inspiration occurs. (Chapter 3)

Vasodilator Agent causing dilation of the blood vessels. (Chapter 21)

Vasopressor Agent causing contraction of the capillaries and arteries. (Chapter 21)

Ventricular fibrillation (VF) Cardiac condition in which normal ventricular contractions are replaced by coarse or fine, rapid movements of the ventricular muscle. (Chapter 21)

Virostatic Stopping a virus from replicating. (Chapter 13)

Virucidal Killing a virus. (Chapter 13)

Virus Obligate intracellular parasite containing either DNA or RNA that reproduces by synthesis of subunits within the host cell and causes disease as a consequence of this replication. (Chapter 13)

Viscosity Resistance of liquid to sheer forces; a rheologic property characteristic of liquids and represented by the loss modulus G'' . (Chapter 9)

X

Xanthine Nitrogenous compound found in many organs and in the blood and urine. (Chapter 8)

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Common Terms and Abbreviations

Term or Phrase	Abbreviation	Meaning	Term or Phrase	Abbreviation	Meaning
	AD	right ear	in vitro	in vit.	in glass
ad	ad	to, up to	maximum	Max	maximum value
ab libitum	ad. lib.	at pleasure	mean value	-, above any symbol	mean or average value
	amp	ampule	misce	m.	mix
	amt	amount	non repetatur	non. rep.	do not repeat
ana	a.a. or aa	of each	oculus dexter	o.d.	right eye
ante cibos	a.c. or ac	before meals	oculus sinister	o.s.	left eye
aqua	aq.	water	omni die	o.d.	daily
	AS	left ear	omni mane	o.m.	every morning
	atc	around the clock	omni nocte	o.n.	every night
	AU	both ears	percentage	%, before any symbol	percentage of the predicted normal value
bis in die	b.i.d.	twice a day	per os	p.o.	by mouth
	BP	blood pressure	placebo	placebo	to please
	bm	bowel movement	post cibos	p.c.	after meals
	BSA	body surface area	pressure	p	pressure in general
	c	centigrade	pro re nata	p.r.n.	as the occasion arises
	CBC	complete blood count	quantum sufficiat	q.s.	sufficient quantity
	cc	cubic centimeter	quarter in die	q.i.d.	four times a day
	caps	capsules	recipe	Rx	take
collyrium	collyr.	eye lotion	semis	ss	one-half
	compd	compound	sine	̄	without
cum	̄	with	si opus sit	s.o.s.	if necessary
cum aqua	cum aq.	with water	ter in die	t.i.d.	three times a day
dentur tales doses	d.t.d.	give such doses	time	T	time indicated
dispensa	disp.	dispense	time derivative	̇, above any symbol	rate of change
	Dx	diagnosis	trochiscus, torchisci	troch.	lozenge, lozenges
et	et	and	unguentum	ungt.	ointment
frequency	F	frequency of any event in time	ut dictumw	ut dict.	as directed
gutta, guttae	gtt.	drop, drops	volume	V	gas volume in general
hora somni	h.s.	at bedtime			

Additional Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
A	alveolar	T	tidal
ATPD	ambient temperature and pressure, dry	$\dot{V}_A$	alveolar ventilation
ATPS	ambient temperature and pressure, saturated	$\dot{V}_{CO_2}$	carbon dioxide production per minute
B	barometric	V'_D	dead-space volume
BTPS	body temperature, pressure saturated	$\dot{V}_{Dalv}$	alveolar dead-space ventilation per minute (BTPS)
D	dead space	$\dot{V}_{Danat}$	anatomic dead-space ventilation per minute (BTPS)
E	expired	$\dot{V}_{Dphy}$	physiologic dead-space ventilation per minute (BTPS)
I	inspired	$\dot{V}_E$	Minute ventilation (expired)
L	lung	$\dot{V}O_2$	oxygen consumption per minute (STPD)
R	respiratory exchange ratio	V_T	tidal volume
STPD	standard temperature, pressure, dry		